AAP Focus on Medicinal Plants Series

Phytochemical Composition and Pharmacy of Medicinal Plants

Volume 1



T. Pullaiah
Editor

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Volume 1

Edited by

T. Pullaiah, PhD

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For millennia, medicinal plants have been a valuable source of therapeutic agents, and still many of today's drugs are plant-derived natural products or their derivatives. Bioactive compounds typically occur in small amounts, and they have more subtle effects than nutrients. The bioactive compounds influence cellular activities that modify the risk of disease and cure and alleviate disease symptoms. The bioactive compounds have potentially important health benefits, and these compounds can act as antioxidants, enzyme inhibitors and inducers, inhibitors of receptor activities, and inducers and inhibitors of gene expression among other actions. A wide array of biological activities and potential health benefits of medicinal plants have been reported, which include antiviral, antimicrobial, antioxidant, anti-cancer, anti-inflammatory, antidiabetic properties as well as protective effects on the liver, kidney, heart, and nervous system.

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Former Professor, Department of Botany, Sri Krishnadevaraya University, Andhra Pradesh, India

T. Pullaiah, PhD, is a former Professor at the Department of Botany at Sri Krishnadevaraya University in Andhra Pradesh, India, where he has taught for more than 35 years. He has held several positions at the university, including Dean of the Faculty of Biosciences, Head of the Department of Botany, Head of the Department of Biotechnology, and Member of Academic Senate. Under his guidance, 54 students earned their doctoral degrees. He was President of the Indian Botanical Society (2014), President of the Indian Association for Angiosperm Taxonomy (2013), and Fellow of the Andhra Pradesh Academy of Sciences. He was awarded the Panchanan Maheshwari Gold Medal, the Prof. P. C. Trivedi Medal, the Dr. G. Panigrahi Memorial Lecture Award of the Indian Botanical Society, and Prof. Y. D. Tyagi Gold Medal of the Indian Association for Angiosperm Taxonomy, and the Best Teacher Award from Government of Andhra Pradesh.

A prolific author and editor, he has authored 52 books, edited 23 books, and published over 330 research papers. His books include *Advances in Cell and Molecular Diagnostics* (published by Elsevier), *Camptothecin, and Camptothecin Producing Plants* (Elsevier), *Ethnobotany of India* (5 volumes, published by Apple Academic Press), *Global Biodiversity* (4 volumes, Apple Academic Press), *Red Sanders: Silviculture and Conservation* (Springer), *Genetically Modified Crops* (2 volumes, Springer), *Monograph on Brachystelma and Ceropegia in India* (CRC Press), *Flora of Andhra Pradesh* (5 volumes), *Flora of Eastern Ghats* (4 volumes), *Flora of Telangana* (3 volumes), *Encyclopedia of World Medicinal Plants* (7 volumes, 2nd edition), and *Encyclopedia of Herbal Antioxidants* (3 volumes). He is currently working on 36 volumes of the new book series *Biodiversity Hotspots of the World*.

Professor Pullaiah was a member of the Species Survival Commission of the International Union for Conservation of Nature (IUCN). He received his PhD from Andhra University, India, attended Moscow State University, Russia, and worked as postdoctoral fellow during 1976–1978.

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Abbreviations

AC-AgNPs	*Ananas comosus* silver nanoparticle
ACE	angiotensin-converting enzyme
ACF	aberrant crypt foci
AChE	acetylcholinesterase
AEALB	aqueous extract of *Anogeissus latifolia* bark
AFCs	antifungal creams
ALP	alkaline phosphatase
ALT	alanine transaminase
AM	*Abelmoschus manihot*
AP-1	activator protein 1
APG	apegenin-7-glucoside
aPTT	activated partial thromboplastin time
AR	aldose reductase
AREE	*Amaranthus retroflexus* leaves
AST	average survival time
AVG	Aloe vera gel
BAL	broncheoalveolar lavage
BChE	butyrylcholinesterase
BHT	butyl hydroxytoluene
BHV-5	bovine herpesvirus type 5
BSA	bovine serum albumin
BWE	boiling water extract
BWP	buckwheat protein
CAA	*Colchicum autumnale* tubers
cAMP	cyclic adenosine monophosphate
CAPs	cell adhesion proteins
CAT	catalase
CBC	cannabichromene
CBD	cannabidiol
CBDA	cannabidiolic acid
CBD-C1	cannabidiocol-C1
CBD-C4	cannabidiol-C4
CBDV	cannabidivarin
CBDVA	cannabidivarinic acid

CBE	cannabielsoin
CBF-C5	cannabifuran-C5
CBG	cannabigerol
CBGM	cannabidiol monomethyl ether
CBL	cannabicyclol
CBN	cannabinol
CBND	cannabinodiol
CBT	cannabitriol
CBV	cannabigerol
CCl4	carbon tetrachloride
CDE	chamomile decoction extract
CDEC	2-chlorallyl diethyldithiocarbamate
CE	chamomile extricate
CEE	cold ethanolic extract
cGMP	cyclic guanosine monophosphatase
CNS	central nervous system
CPE	cytopathic effect
CRF	corticotropin-releasing factor
CTV	citrus tristeza virus
CV	cobra venom
cysLT	cysteinyl Leukotriene
DAL	Dalton’s ascitic lymphoma
DCBF-C5	dehydrocannabifuran
DCI	d-chiro-Inositol
DDR	defect depth reduction
D-GalN	d-galactosamine
DLA	Dalton’s lymphoma ascites
DM	1,2-dimethylhydrazine
DMH	dimethylhydrazine
DPP IV	dipeptidyl peptidase IV
DPPH	1,1-diphenyl-2-picryl hydrazyl
EA	ethyl acetate
EAC	Ehrlich ascites carcinoma
EAEC	enteroaggregative E. coli
EDAX	energy dispersive X-ray analysis
EMCV	encephalomyocarditis virus
EOs	essential oils
EPMC	ethyl p-methoxycinnamate
EPP	ethyl phenylpropiolate
ERK-2	extracellular regulated kinase-2

ETEC	enterotoxigenic E. coli
FAO	Food and Agriculture Organization
FRAP	ferric reducing antioxidant power
fT3	free triiodothyronine
fT4	free thyroxine
FTIR	Fourier transform infrared spectroscopy
GABA	gamma amino butyric acid
GAD	generalized anxiety disorder
GAE	gallic acid equivalent
GC-MS	gas chromatography-mass spectrometry
GMCSF	granulocyte-macrophage colony-stimulating factor
GOT	glutamate oxaloacetate transaminase
GPCR	G-protein coupled receptor
GPT	glutamate pyruvate transaminase
GSH	glutathione
GST	glutathione S-transferase
H2O2	hydrogen peroxide
HAM-A	Hamilton anxiety rating
HBSS	Hank's balanced salt solution
HDL	high-density lipoproteins
HDL-C	high-density lipoprotein cholesterol
HF	human foreskin
HIV	human immunodeficiency virus
HKC	Huangkui capsule
HL60	human leukemia
HONE-1	human nasopharyngeal carcinoma
HP	*Helicobacter pylori*
HPLC	high-performance liquid chromatography
HSS	hyperthyroid symptom scale
HSV	herpes simplex virus
HTPS	high-throughput pharmacological screening
ICAM-I	intracellular adhesion molecule-I
IFN-γ	interferon gamma
IL-2	interleukin-2
IL-8	interleukin-8
iNOS	inducible nitric oxide synthase
IYR	international year of rice
KPC	*K. pneumoniae carbapenemase*
LA	lipoic acid
Lc-EA	*L. chinensis* ethyl acetate

LDL-C	low-density lipoprotein cholesterol
LOX-1	lipoprotein receptor 1
LPO	lipid peroxidation
LPS	lipopolysaccharide
MA	methyl alcohol
MAO-A and MAO-B	monoamine oxidase A and B
MAP	modified aloe polysaccharide
MBC	minimum bactericidal concentration
MCE	*M. chamomilla* ethanolic
MDA	malondialdehyde
MES	maximal electroshock
MFC	minimum fungicidal concentration
MI	myocardial infarction
MIAs	monoterpenoid indole alkaloids
MIC	minimum inhibition concentration
MMP	matrix metalloproteinase
MN	micronuclei
MPBL	methanolic extract of pipe betle leaves
MPO	myeloperoxidase
MrBBS	*Matricaria recutita* α-bisabolol synthase
MWS	morphine withdrawal disorder
NaOCl	sodium hypochlorite
NARI	National Agricultural Research Institute
NL	neutral lipids
NMR	nuclear magnetic resonance
NO	nitric oxide
NSAIDs	nonsteroidal anti-inflammatory drugs
ORAC	oxygen radical scavenging activity
OVA	ovalbumin
PAGE	polyacrylamide gel electrophoresis
PBMC	peripheral blood mononuclear cells
PBSA	Poisson–Boltzmann calculations
PE	petroleum ether
PGD2	prostaglandin D2
PHA	phytohemagglutinin
pI	isoelectric point
PLA2	phospholipase 2
PNG	Papua New Guinea
PPP	polyphoretin phosphate

PT	*Piper trioicum*
PT	prothrombin time
PTP1B	protein tyrosine phosphatase-1B
PTZ	pentylenetetrazole
PZQ	praziquantel
QMTs	quinone-methide triterpenoids
rBTI	recombinant buckwheat trypsin inhibitor
RE	retinol equivalents
RMP	*Rhizophora mucronata* polysaccharide
ROCs	receptor-operated Ca2+ channels
ROS	reactive oxygen species
RP-HPLC	reversed-phase high-performance liquid chromatographic
SCFAs	straight-chain fatty acids
SD	steam distillation
SDH	sorbitol dehydrogenase
SE	solvent extraction
SEM	scanning electron microscopy
SERM	selective estrogen receptor modulators
SFE	supercritical fluid extraction
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOD	super oxide dismutase
SSEDIKE	Ser-Ser-Glu-Asp-Ile-Lys-Glu
STZ	streptozotocin
STZ-NIN	streptozotocin-nicotinamide
TBARS	thiobarbituric acid reactive substances
TEO	turmeric essential oil
TFA	total flavones of *A. manihot*
TFC	total flavonoid content
TFlavC	total flavanol content
TGF	transforming growth factor
TL	transfer latency
TLR2	toll-like receptor 2
TNF	tumor necrosis factor
TNFα	tumor necrosis factor-alpha
TPA	total phenolic acid
TPC	total phenolic content
TRP	transient potential profile

TT	thrombin time
TTriC	total triterpenoids content
USFDA	United States Food and Drug Administration
VDCs	voltage-dependent Ca^{2+} channels
WHO	World Health Organization
XR	X-ray diffraction method
Δ^8-THC	Δ^8-trans-tetrahydrocannabinol
Δ^9-THC	Δ^9-tetrahydrocannabinol

Preface

Many young researchers used to approach me with the question, 'Can you suggest to me a medicinal plant on which I can work?' To answer this question, I had to dig out the literature on the bioactive and pharmacology of medicinal plants. During this search, I found that a comprehensive review of Phytochemical composition and pharmacy for many medicinal plants is not available. With a view to filling this gap, we started this series of 10-volume book series on Bioactives/Biomolecules/Phytochemistry and Pharmacology of Medicinal plants. This is the last book in this series. A comprehensive review of more than 80 plant species is given in this two-volume book.

In each chapter, a brief introduction about the species is given. Bioactive phytochemicals from the plant are then listed, and their chemical structures are given. It is followed by Pharmacological activities. All the published literature on the pharmacological activities of that species is reviewed. A wide array of biological activities and potential health benefits of the medicinal plant, which include antiviral, antimicrobial, antioxidant, anti-cancer, anti-inflammatory, and antidiabetic properties, as well as protective effects on the liver, kidney, heart, and nervous system, are given.

Many contributors to this book are young researchers, mostly research scholars. In many cases, the manuscripts have been revised three to four times. Publishers insisted on bringing down the plagiarism to 5%, which was a tough task because chemical names, disease names, and methods couldn't be modified. In spite of this, plagiarism was brought down to nearly 5%. I thank both publishers and contributors for the same.

I hope that this will be a sourcebook for the development of new drugs. I request the readers to give their suggestions for improvement of the coming volumes and the next edition.

I wish to express my grateful thanks to all the authors who contributed to the review chapters.

CHAPTER 1

Phytochemistry and Ethnopharmacological Review of Autumn Crocus (*Colchicum autumnale* L.)

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1.1 INTRODUCTION

Colchicum autumnale L. belongs to the family Colchicaceae. *Bulbocodium autumnale* (L.) Lapeyr., *C. commune* Neck., *C. crociflorum* Sims, *C. bulgaricum* Velen., *C. drenowskii* Degen & Rech.f. ex Kitan., *C. vernale* Hoffm., *C. pannonicum* Griseb. & Schenk, *C. orientale* Friv. ex Kunth, *C. polyanthon* Ker Gawl., *C. rhodopaeum* Kov., *C. praecox* Spenn., and *C. transsilvanicum* Schur are the synonyms for this species (POWO, 2019; www.theplantlist.org). This plant's local/vernacular names include Autumn crocus, Meadow saffron, Colchique, Surinjan Shirin, Hirantutiya, etc.

Autumn crocus is an annual herb with underground tunicate poisonous bulbs. Leaves few, appears usually in spring, lanceolate, size 25 × 5 cm. Flowers 1–3, rose-purple in color, appear in autumn season; perianth funnel-shaped with slender pedicel-like tube and expands above into a 5 cm wide

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limb; segments 2.5 to 7 cm long. Stamens 6, less than half of the length of the segments. Capsule 2.5 to 3.8 cm arising with foliage in spring. It is native to Belgium, Albania, Bulgaria, Austria, France, Czechoslovakia, Great Britain, Germany, Hungary, Greece, Italy, Ireland, Poland, Netherlands, Spain, Romania, Ukraine, Switzerland, and Yugoslavia. It has been introduced to New Hampshire, Baltic States, Kentucky, Denmark, North Carolina, New Zealand South, Oregon, Northwest Europe, Utah, Sweden, and Vermont (POWO, 2019).

The plant name '*Colchicum*' came from the term '*Colchis*' or '*Kolchis*,' an ancient Georgian kingdom, where these plants were widely spread in the eastern part of the Black Sea. The medicinal use of the plant bulb was reported first time in the first century AD and recommended by Byzantine physician, Alexander of Tralles. Later, it was used to treat Behcet's syndrome, Sweet's syndrome, scleroderma, amyloidosis, liver cirrhosis, and gout. In the Ayurveda and Unani system of medicines, it is the most useful agent to heal internal injuries, backache, gout, and muscular, and joint pains; but it greatly causes intestinal pain followed by vomiting and purging. The extracted colchicine, in the form of a tablet, is used to treat several inflammatory conditions such as arthritis, gouty attacks, Behcet's syndrome, serositis related to familial Mediterranean fever, in the prevention of acute and recurrent pericarditis cases, and also after the cardiac surgery. Recent studies have revealed that the plant bulb and seeds are used as medicine for enlarged prostate, dropsy, gout, rheumatism, and arthritis. The plant is also used to treat foot-palm burning, inflammations, jaundice, sciatica, tumor, myeloid leukemia, gonorrhea, and ascites, as well as to treat sexual impotence (Imazio et al., 2009; Akram et al., 2012; Kumar et al., 2017; Siddiqui and Akhtar, 2018; Davoodi et al., 2021).

1.2 BIOACTIVES

Ellington et al. (2003) established a supercritical CO_2 extraction method to extract alkaloids such as colchicine, colchicoside, and 3-demethylcolchicine from the wild *Colchicum autumnale* seeds. Several parameters, such as temperature, pressure, percentage of modifier, and extraction time, were assessed. Constant carbon dioxide density (0.90 g/mL) and 1.5 mL/min flux, 110 min extraction time, and 3% methanol as modifier were the optimum conditions for maximizing the recovery of alkaloids. The quantitative determination of alkaloids using HPLC instrumentation revealed a 98% recovery

of the alkaloids. A comparative account of several conventional methods of extractions was also carried out, including maceration and ultrasonication, wherein the same contents were recorded. In the study, colchicine content was found highest (0.84 ± 0.02–0.85 ± 0.01%), followed by colchicoside (0.56 ± 0.02–0.57 ± 0.02%) and 3-demethylcolchicine (0.08 ± 0.02–0.11 ± 0.02%).

Rueffer and Zenk (1998) noted microsomal preparations from separated immature seeds of *C. autumnale*. Crude microsomal preparations were incubated with O-methylandrocymbine and NADPH (labeled with ^{14}C) to examine the ring expansion reactions. It formed a newly labeled product with a 54% yield and similar to the *Rf* of compound demecolcine. Additionally, the conversion of demecolcine to colchicine in the presence of NADPH and acetyl-CoA was also investigated. It was found that the formation of the product was certainly dependent on NADPH and O-methylandrocymbine (unlabeled) with 50% saturations at 75 and 60 μM concentrations, respectively. No transformation was observed in the absence of NADPH and boiled enzyme. The pH 8.5 was found optimum for the reaction and 90% reaction was inhibited by gassing the mixture with carbon dioxide and oxygen (9:1). Mixture of nitrogen and oxygen (9:1) gasses failed to inhibit the reaction and it reversed the inhibition up to 60% due to white light, which supported the involvement of cytochrome P-450 enzyme. The authors also noted that the addition of cytochrome c inhibited the reaction (50%) at 40 μM concertation. Further, the authors proposed the ring expansion reaction that could be preceded by a hydroxylation reaction at C-12 of O-methylandrocymbine.

Three *Colchicum* species such as *C. speciosum*, *C. robustum*, and *C. autumnale* are the important ingredients of many herbal preparations since they are the rich source of tannins, flavonoids, phenolics, and tropolone alkaloids. HPLC analysis of these *Colchicum* species indicated the presence of colchicine, 3-demethyl colchicine, colchicoside, demecolcine, colchifoline, 2-demethyl colchicine, cornigerine, and N-deacetyl-N-formyl colchicines. It revealed the presence of several tropolone alkaloids from the corm of *C. autumnale viz.* colchicine (445.92 ± 1.09 mg/100 g), colchicoside (15.75 ± 0.67 mg/100 g), 2-demethyl colchicine (7.16 ± 0.47 mg/100 g), 3-demethyl colchicine (33.23 ± 1.23 mg/100 g), colchifoline (46.26 ± 1.21 mg/100 g), demecolcine (261.51 ± 1.45 mg/100 g), N-deacetyl-N-formyl colchicine (63.69 ± 0.58 mg/100 g) and cornigerine (39.27 ± 0.29 mg/100 g) (Davoodi et al., 2021).

Malichova et al. (1979) studied the alkaloid content in fresh as well as dried flowers and leaves of *C. autumnale*. The study revealed that 2- and

3-demethylated derivatives of colchicine were absent in extracts prepared from fresh materials, but they were found in considerable quantity in shade-dried material. In addition to the known alkaloids, authors found several other compounds such as cornigerine, 2- and 3-demethyl-N-deacetyl-N-formylcolchicine, 2- and 3-demethyl-demecolcine, as well as a new alkaloid 2-de-methylcolchifoline. In the study, no alkaloid was detected without a tropolone ring. Authors had an opinion that instead of using seeds and corms to isolate the colchicine alkaloids commercially, it is better to use properly dried leaves and flowers which are easy to obtain. It was observed that the seed alkaloid contents especially the colchicine and colchicoside varied regionally and this variation remained stable when the corms of this plant were cultivated in the same field collected from different natural sites (Poutaraud and Girardin, 2005a).

Poutaraud and Girardin (2005b) studied intra- and inter-genetic variations along with variations in the contents of colchicine, 3-demethylcolchicine, and colchicoside in six accessions of domesticating *C. autumnale*, collected from natural habitats in eastern France. Parameters like seed dry weight per plant, colchicine: colchicoside ratio, inter-accession variability, and alkaloid content were recorded. The results suggested that the improvement in the alkaloid content, as well as shoot dry weight by 80 and 300%, could be possible through the vegetative propagation of selected genotypes (Figure 1.1).

1.3 PHARMACOLOGY

1.3.1 T-CELL ACTIVATION AND EFFECTOR FUNCTIONS

The mitogenic activities of plant lectins play an important role in studying T-cell activation and effector functions. Bemer et al. (1996) isolated an agglutinin substance from the *Colchicum autumnale* tubers (CAA), which exhibited the proliferation of murine lymphocytes. The binding of all T- and B-lymphocytes to CAA was revealed by the pilot experiments and the spleen cells were stained with PE-anti-CD4 and PE anti-CD8 mAbs antibodies to analyze the CAA binding to the T subset (Bemer et al., 1996). The activation markers such as CD44 and CD69 were used to trigger the T-cell and the capability of CAA to activate the T-cells has been verified. Further, the expression of CD44 and CD69 was analyzed by culturing the spleen cells with CAA, labeled with PE-anti-CD4 or PE-anti-CD8 mAbs antibodies, and

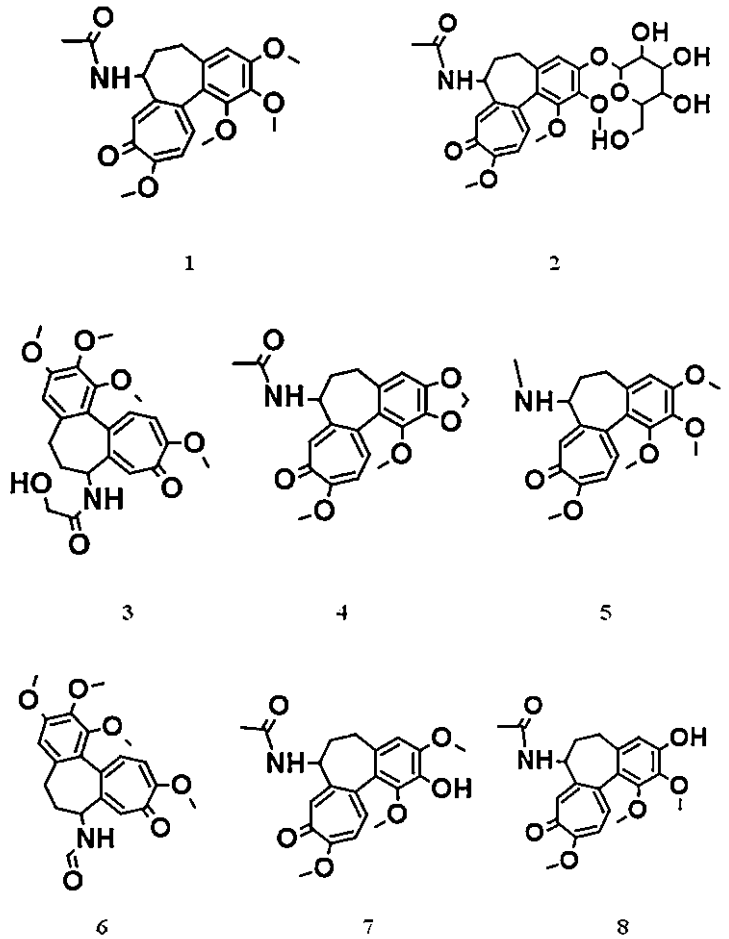


FIGURE 1.1 Structures of colchicine (1); colchicoside (2); colchifoline (3); cornigerine (4); demecolcine (5); glulisine (6); 2-demethyl colchicine (7); and 3-demethyl colchicine (8).

they were recovered at a specified time. It was found that the density of these two markers was significantly high at 72 hours. The expression of two activation markers such as CD44 and CD69 showed that they were expressed in the range of 90–94% by the T-cells. It revealed the binding capability of CAA by provoking the activation of all the T-cells and it positively triggered the expression of CD44 and CD69 markers at 48 hours. Based on the study, authors concluded that two T-cell subsets were clearly delimited by the binding of a T-cell mitogen CAA and as a result, the unrestricted

activation of all the T-cells, the culmination in the expression of CD44 and CD69 activation markers and induction of α-chain of the IL2 receptor is completely restricted (Bemer et al., 1996).

1.3.2 ANTICANCER ACTIVITY

Colchicine is a tubulin-targeting compound that inhibits microtubule formation by targeting fast-dividing cells. Necrosis and selective pro-death autophagy in human cancer cells were induced by two selective analogs *viz.* Green 1 [(S)-3,8,9,10-tetramethoxyallocolchicine] and N-acetyl-O-methylcolchinol (NSC 51046) (Larocque et al., 2014). In the studied analogs, NSC 51046 was non-selective as it could induce apoptosis in pancreatic cancer cells such as PANC-1 and BxPC-3 and normal human fibroblast cells. However, the pro-death autophagy in these pancreatic and E6-1 cancer cells was moderately induced by Green 1, but it failed to express its activity in normal human fibroblasts. Unlike colchicine and NSC 51046, Green 1 did not affect tubulin polymerization. It downregulated the human cancerous T cell proliferation and integrity of the cell membrane, but it completely failed in inducing apoptosis in pancreatic cancerous cells. However, NSC 51046 exhibited cell shrinkage, nuclear condensation, apoptosis, and cell blebbing in both the pancreatic cancer cells along with normal fetal fibroblasts. An increase in the reactive oxygen species (ROS) was also found in the mitochondria of pancreatic cancer cells due to the activity of the Green 1 analog. It could be a better lead in cancer therapy as it is highly tolerated in the experimental mice, and in fact, it changed its mechanism of action and improved selectivity with a minute structural modification (Larocque et al., 2014).

Colchicine is a known and potent microtubule targeting agent, but its therapeutic application against cancer is very limited due to its toxic effects in normal cells. Bhattacharya et al. (2016) found the efficacy of the compound at a less toxic dose of 2.5 nM in A549 cells, and it did not cause any G2/M arrest in the targeted cells. However, it strongly delayed the process of reformation in the spindle microtubules and induced ROS-mediated autophagy, followed by senescence in A549 cells. Authors assumed that the toxic effect of colchicine in A549 cells was sensitized by autophagy inhibitor 3-methyladenine enzyme (3-MA) through switching senescence to apoptotic death and this combinational effect reduced the toxicity of the compound in normal lung fibroblasts (WI38).

1.3.3 COLCHICINE AND HUMAN TUBULIN INTERACTION

Spasevska et al. (2017) investigated the interaction of the compound β-tubulin of *C. autumnale* along with the colchicine through molecular modeling, comparative genomics, and computational studies using Poisson–Boltzmann calculations (MM/PBSA). The authors carried out the multiple sequence alignment between the selected sequences of *C. autumnale* α- and β-tubulin and the human α- and β-tubulin isoforms. Primary structures for the colchicine-binding domain and full-length proteins were analyzed simultaneously. These findings revealed 93 and 96% sequence similarities for both α and β tubulins, respectively. A higher percentage of identity (86%) and similarity (94%) were found between the human and *C. autumnale* tubulins through the colchicine-binding domains. The comparison of the molecular model between *C. autumnale* and human tubulin dimer clearly revealed that colchicine resistance is related to amino acid substitutions. In contrast to this, the higher colchicine resistance for *C. autumnale* over the human tubulin was confirmed by non-significant disruption of MT dynamics. The study suggested the variability in the amino acid sequences, which are not crucial for the binding of colchicine to human β-tubulin and *C. autumnale*, but this mechanism was found as a characteristic feature of the evolutionary trend (Spasevska et al., 2017).

1.3.4 THERAPEUTIC REGULATIVE EFFECT

Scheffer et al. (2016) performed an observational study on 24 goiter patients treated with *C. autumnale*, as the plant was used for various thyroid disorders in anthroposophic medicine. The patients were suffering from suppressed TSH levels, free thyroxine (fT4), and normal/slightly elevated free triiodothyronine (fT3) levels. Pathological investigations were conducted after 3, 6, and 12 months of *C. autumnale* treatment, where parameters such as TSH, fT4 and fT3 hormonal status, hyperthyroid symptom scale (HSS), and thyroid volume were considered. After the treatment with *C. autumnale*, it showed a decrease in median HSS from 4.5 to 2 and fT3 from 3.85 to 3.45 pg/mL. A significant reduction in thyroid volume (13.9%) and TSH were also noted. The effect of CAU on TSH and fT3 hormones were found through linear regression, and it effectively changed the clinical pathology of hyperthyroidism and thyroid volume in patients with goiter by regulating the thyroidal hormones effectively.

KEYWORDS

- ***Bulbocodium autumnale***
- ***Colchicum autumnale***
- **hyperthyroid symptom scale**
- **pharmacology**
- **Poisson–Boltzmann calculations**
- **colchicine**

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CHAPTER 2

Bioactive Constituents and Pharmacological Activity of *Citrullus colocynthis* (L.) Schrad.

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2.1 INTRODUCTION

Citrullus colocynthis (L.) Schrad is the perennial desert vine plant belonging to the family Cucurbitaceae. The species has two synonyms, *Citrullus vulgaris* L. and *Cucumis colocynthis* L. It is commonly known as Bitter apple, Bitter cucumber, Equsi, and Vine of Sodon (English) Badi Indrayan (Hindi), Indrayan, Indrabaruni, Panjot (Bengali), Hamekkae (Kannada), Kattuvellari (Malayalam), Kadu-Indrayani (Marathi), Atmaraksha, Brihatphala, Brihadvaruni (Sanskrit), Petikari (Tamil), Chittipapara (Telugu), Shahme-Hinzal, Indyrayan (Urdu), etc. *C. colocynthis* is a vine plant of the arid region which grows well in sandy soil. It is originated from Asia and Mediterranean Basin, especially Turkey and Nubia, which further distributed in the western coastal region of Africa, the Sahara, and Egypt in the eastern region. Through India, it also reaches the northern coastal region of the Caspian and Mediterranean seas. The presence of species has been

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also found in European countries located in the south such as the islands of the Grecian archipelago and Spain (Pravin et al., 2013; Hussain et al., 2014; Bhasin et al., 2020). It is a dioecious trailing herb that grows abundantly in sandy arid soils. Leaves are comparably similar to watermelon leaves with fine green upper and pale colored lower surface, palmed, angular with 3–7 divided lobes. *C. colocynthis* bears both male and female flowers, which are yellowish in color and solitary, present at the axes of leaves. Fruits are small, orange-sized, thick, globular, greenish, mottled, whitish when ripe, and encompass light and inner spongy bitter pulp. Seeds are numerous, smooth, and pale brown in color, small in size (4–6 mm long) oblong, ovate, and compressed, which is thrown away before the pulp is used (Pravin et al., 2013). The rind is brittle and breaks into three wedge-shaped pieces; the inner surface of the rind is covered with a soft, spongy, white substance that tastes intensely bitter. All parts of the plant are bitter and odorless. *C. colocynthis* is broadly used for the treatment of a number of diseases, including diabetes, constipation, leprosy, asthma, bronchitis, jaundice, joint pain, cancer, and mastitis, etc., in the indigenous system of medicines (Abo et al., 2008; Asyaz et al., 2010).

2.2 BIOACTIVES

Various phytochemical constituents, such as carbohydrates, proteins, amino acids, alkaloids, flavonoids, terpenoids, etc., are reported from the entire *C. colocynthis* (Kalva et al., 2018). Ardekani et al. (2011) isolated major phytochemicals from *C. colocynthis* pulp are pectin, colocynthin, colocynthein, whereas fixed oil and albuminoids from seeds. *C. colocynthis* fruits are considered a vital source of drugs. Likewise, the investigation on fruit extract was conducted by Yoshikawa et al. (2007) and Vakiloddin et al. (2015) and reported some important compounds, i.e., cucurbitacin A, B, C, D, E, I, J, K, L, flavonoids, alkaloids, fatty acids, glycosides, colocynthosides A and B. Similarly, the two novel cucurbitacins were also reported by Sung et al. (2015) from ethyl acetate (EA) fruit extract of *C. colocynthis viz.*, cucurbitacin 2-O-D-glucopyranosyl and elaterin-2-D-glucuopyranoside (coloside A). Kumar et al. (2008) also reported two tetracyclic cucurbitane-type triterpene glycosides from the EA of leaves. Several other important compounds, including, Isosaponarin, Isovitexin, Isoorientin 3-o-methyl ether, Catechin, Myricetin, Quercetin, Kaempferol, Gallic acid, p-Hydroxybenzoic acid, Ferulic acid, and Sinapic acid were also isolated from different plant parts, i.e., fruits, seeds, and pulp (Meena and Patni, 2008; Hussian et al., 2013). The seeds of *C. colocynthis* were also analyzed for oil content, which ranges between 17% and 19%, mainly composed of 67–73% linoleic acid, 10–16%

oleic acid, 9–12% palmitic acid, and 5–8% stearic acid. The aqueous rind extract comprised of glycosides, saponins, tertiary, and quaternary alkaloids (Gurudeeban et al., 2010). The chemical structure of some important bioactive compounds of *C. colocynthis* is mentioned in Figure 2.1.

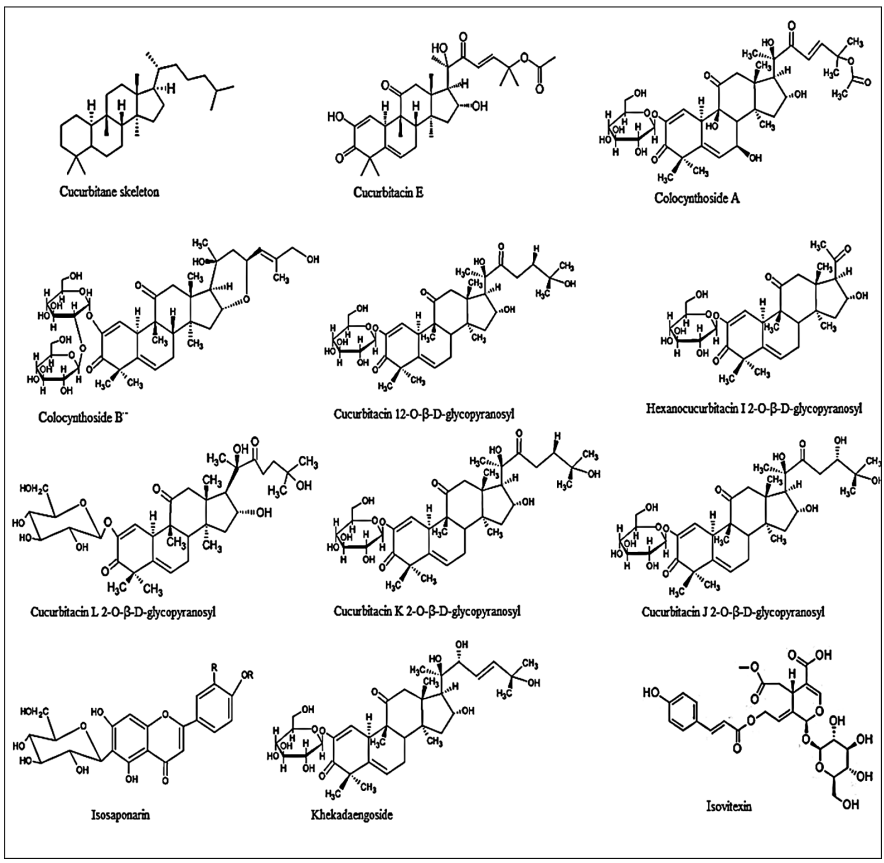


FIGURE 2.1 Chemical structure of important bioactive components of *Citrullus colocynthis* (L.) Schrad.

2.3 PHARMACOLOGY

2.3.1 ANTIDIABETIC ACTIVITY

C. colocynthis has been extensively used as an antidiabetic medication in tropical and subtropical countries. Al-Gaithi et al. (2004) examined the effect of the aqueous extract of *C. colocynthis* seed on the biochemical parameters of normal and streptozotocin (STZ)-induced diabetic rats and concluded

that oral administration of the plant extract reduced the plasma level of AST and LDH significantly with amelioration of the toxic effects of STZ. Abdel-Hassan et al. (2000) investigated the effects of aqueous, glycosidic, alkaloidal, and saponin extracts of rind on the plasma glucose levels in normal rabbits, while the effects of saponin extract on the fasting plasma glucose levels in alloxan-induced diabetic rabbits. In normal rabbits, oral administration of the aqueous extract (300 mg kg^{-1}) produced a significant reduction in plasma glucose after 1 h and highly significant after 2, 3, and 6 h.

Jayaraman et al. (2009) investigated the effect of petroleum ether (PE) extract of *C. colocynthis* fruits on depressing the blood glucose levels and thiobarbituric acid reactive substances (TBARS) in STZ induced Diabetic albino rats. The effect of pulp hydro-ethanol extract on alloxan-induced hyperlipidemia in 24 albino diabetic rats (150 to 200 g) was investigated by Dallock (2011) for a period of 30 days. It showed a significant reduction in total cholesterol, triglycerides, free fatty acids, and phospholipids in serum and liver. This study indicated that pulp hydro-ethanol extract possesses strong hypolipidemic and antioxidant actions in alloxan-induced diabetic rats.

2.3.2 HYPOLIPIDEMIC ACTIVITY

Rahbar et al. (2010) evaluated the hypolipidemic effect of *C. colocynthis.* The investigation was performed on 100 dyslipidemia patients with two groups (treated and placebo) and was daily treated with seed powder (300 mg) for six weeks. A significant difference was observed within and between treated and placebo groups. They concluded that a daily intake of 300 mg seed powder can lower the triglyceride and cholesterol concentration significantly in nondiabetic hyperlipidemic patients. Another investigation was performed by Darakda et al. (2007) to see the effect of *C. colocynthis* 70% ethanolic extract on the lipid profile of Rabbits. The plant extract was orally given to atherogenic rabbits and the increased cholesterol levels were brought to normal. The phospholipids and triglycerides levels were also reduced.

2.3.3 ANTIMICROBIAL ACTIVITY

Antimicrobial effects in *C. colocynthis* extracts varied from population to population (Marzouk et al., 2009) and the extracts were active against both gram-positive and gram-negative bacterial strains (Marzouk et al., 2010a,

b). Menon et al. (2003) displayed the inhibitory effect of the ethanol extract of *C. colocynths* fruit against *Bacillus subtilis* bacteria. Najafi et al. (2010) also evaluated the antimicrobial activity of water and ethanolic leaves and fruit extract of *C. colocynthis* against *Staphylococcus aureus* and the inhibitory effects were compared with standard antibiotic, novobiocin. The ethanolic extract showed inhibitory activity against *S. aureus* more than the water extract. They indicated that 5 mg mL^{-1} ethanolic extract of fruits has a similar inhibitory effect with novobiocin against standard strain. They suggested that the components that existed in ethanolic extract *viz*., alkaloids, flavonoids, and glycosides are more antibacterial effect than novobiocin, especially against hospital-isolated strains. Sharma et al. (2010) also evaluated the antibacterial effect of *C. colocynthis* and *Tribulus terrestris* extracts against various pathogenic bacteria, i.e., *Bacillus cereus, Escherichia coli, Mycobacterium smegmatis, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus* and, *S. epidermidis.* The extracts showed broader and moderate MIC against all the bacterial pathogens ranging from 20–100 µg mL^{-1}.

2.3.4 ANTI-INFLAMMATORY ACTIVITY

Marzouk et al. (2010a) performed the study on the anti-inflammatory activity of *C. colocynthis* fruit aqueous extract (4 mg kg^{-1}) using the carrageenan-induced paw edema assay in rats. Another investigation completed by Aly and Naddaf (2006) on albino rats using carrageenan-induced paw edema also reported the anti-inflammatory activity of *C. colocynthis.* They concluded that the *in vivo* anti-inflammatory action of different types of extracts produced a percent reduction in edema (45.39%), hydrolyzed extract (54.11%), and acetylated extract (64.95%), while Voltaren emulgel produced 63.35%, and suggested that acetylated colocynth extract can be used as a strong anti-inflammatory agent.

2.3.5 ANTIOXIDANT ACTIVITY

The flavonoids, isosaponarin, isovitexin, and isoorientin 3'-O-methyl ether, isolated from the fruits of *C. colocynthis* showed significant antioxidant properties (Delazar et al., 2006). The therapeutic effects of *C. colocynthis* are usually attributed to their polyphenolic compounds, i.e., polyphenol, and plant sterol (Sebbagh et al., 2009). Studies indicated that *C. colocynthis* pulp

extract has potent hypolipidemic and antioxidant effects which help in the reduction of the lipid content of both serum and liver of alloxan-induced diabetic rats. The extract also decreases the level of lipid peroxidation (LPO) markers and the increase in enzymatic and non-enzymatic components of the oxidative system of the liver (Dallak, 2011). Flavonoids are responsible for the antioxidant as well as other biological activities in *C. colocynthis* (Benariba et al., 2013). Studies conducted on the fruit extracts of *C. colocynthis* revealed the presence of phenolic compounds (phenolics and flavonoids) in methanolic fruit extract of *C. colocynthis* with strong free radical scavenging activity (2,500 µg mL^{-1}) and the ability to prevent LPO and radical chain reactions with an increase in free radical scavenging activity of fruit when the concentration of the extract was increased at 2.5 g mL^{-1} (Kumar et al., 2008; Asghar et al., 2011). *C. colocynthis* seeds collected from Tunisia showed IC_{50} of 0.021 mg mL^{-1} with maximum potency (Marzouk et al., 2010b). Therefore, the consequence of these studies strongly supported the use of *C. colocynthis* as a natural antioxidant agent.

2.3.6 ANTICANCER ACTIVITY

Several studies are available on the antiproliferative activities of *C. colocynthis* extracts with different isolates (Liu et al., 2008a, b). Tannin-Sptiz et al. (2007b), reported that treatment of human breast cancer cells with cucurbitacin glucosides, extracted from *C. colocynthis* leaves inhibited the growth of ER (+) MCF-7 and ER (–) MDA-MB-231 cancer cell lines. Which resulted in an accumulation of cells at the G(2)/M phase of the cell cycle, and the treated cells showed a rapid reduction in key protein complex necessary for the regulation of G(2) exit and initiation of mitosis (p34(CDC2)/cyclin B1 complex). Similarly, Liu et al. (2008b) also reported that cucurbitacin B (1–100 µM) inhibited cellular proliferation in a dose and time-dependent manner when applied to a human laryngeal cancer cell line (Hep-2).

2.3.7 CYTOTOXIC ACTIVITY

The cytotoxic effect of *C. colocynthis* fruits was evaluated by Mukherjee and Patil (2012) in two phases through the Brine shrimp lethality bioassay method and was observed that fruit extracts have strong cytotoxic action. Similarly, Tannin-Spitz et al. (2007) reported that the Cucurbitacin B isolated from *C. colocynthis* inhibited (50%) growth (ED_{50}) of 5 human GBM cell

lines in liquid culture and showed a prominent anti-proliferative activity on GBM cells.

2.3.8 INSECTICIDAL ACTIVITY

Torkey et al. (2009) analyzed the insecticidal activity of *C. colocynthis* fruits' different solvent extracts (n-hexane, methylene chloride, chloroform, and ethanol) against *Aphis craccivora* under *in vitro* conditions. Results suggested that the ethanolic extract provides the maximum insecticidal activity compared to other solvent extracts.

2.3.9 ANTIALLERGIC ACTIVITY

The methanolic extract prepared from *C. colocynthis* fruits was evaluated by Yoshikawa et al. (2007) for *a* type I allergic model on mice. It showed an inhibitory effect on ear passive cutaneous anaphylaxis reactions. In addition, the principal cucurbitane-type triterpene glycoside, cucurbitacin E 2-O-b-D-glucopyranoside, and its aglycon, cucurbitacin E, exhibited antiallergic activity.

2.3.10 ANALGESIC ACTIVITY

Marzouk et al. (2010a) investigated the acute toxicity of different parts of *C. colocynthis* and to screen the analgesic and anti-inflammatory actions of aqueous extracts prepared from root stem fruits and seeds at different stages of maturation. All the extracts have analgesic and anti-inflammatory activities at different doses without inducing acute toxicity. The maximum inhibitory activity was observed in immature fruits followed by seeds, while the stem and root extracts possess the less significant inhibitory activity against analgesic models. *C. colocynthis* extract has been also evaluated for analgesic activity by Heydari et al. (2016) who reported a reduced level of pain in individuals with painful diabetic polyneuropathy. Several authors also highlighted that the therapeutic applications of the compounds in *C. colocynthis* are due to anti-inflammatory and analgesic ingredients (Marzouk et al., 2010; Pashmforosh et al., 2018; Meybodi, 2020).

2.3.11 EFFECT ON HAIR GROWTH

Roy et al. (2007) have undertaken a study to evaluate PE and ethanol extracts of *C. colocynthis* for their action on hair growth in albino rats. The extracts were applied on the surface of naked skin for 7 days at 5% concentration, and the time for initiation as well as completion of the hair growth cycle was noted. The initiation period of hair growth was reduced to half, and the time for complete hair growth, bringing a greater number of hair follicles was successfully observed in PE extracts compared to the control.

2.3.12 REPRODUCTIVE EFFECT

The antifertility effects of *C. colocynthis* were evaluated by Chaturvedi et al. (2003) using 50% crude ethanol extract, which was given orally to male albino rats. The treated animals were divided into five groups including A (control), B, C, D, and E. Groups B, C, and D were treated with (100 gm kg^{-1} day^{-1}) extract for 20, 30, and 60 days, while group E received (100 gm kg^{-1} day^{-1}) dose for 60 days and followed by 60 days recovery. At the end of the investigation, they concluded that the 50% ethanol extract showed antiandrogenic nature, thereby reducing reversible infertility in male albino rats. Similarly, the investigation was conducted by Qazan et al. (2007) on the reproductive system of female Sprague-Dawley rats (250–300 g) for 4 and 12 weeks. A total of 20 animals were selected for the study having two groups (10 in each group) and was administered with the dose of *C. colocynthis* extract (400 mg kg^{-1} body weight). The results indicated that long-term exposure of female rats to *C. colocynthis* extract causes adverse effects on the reproductive system and fertility.

2.3.13 ANTIARTHRITIC ACTIVITY

Biswal (2016) conducted an investigation on hydroalcoholic fruit extract of *C. colocynthis* against anti-arthritic activity by using the paw edema method and membrane markers (AST and ALT). The hydroalcoholic extract has shown significant anti-arthritic activity due to some sort of phytochemicals such as flavonoids. Similarly, Venkatraman et al. (2019) evaluated the effect of *C. colocynthis* on type II collagen-induced arthritis-mediated diabetes in Wistar rats and they concluded that *C. colocynthis* extract could be used to improve arthritis by reducing the inflammatory factors such as TNF-α and

IL-6. While further investigations are required to determine the effect of *C. colocynthis* extract on signal transduction in animal models.

KEYWORDS

- **antidiabetic activity**
- **bioactives**
- ***Citrullus colocynthis***
- ***Citrullus vulgaris***
- **streptozotocin**
- **thiobarbituric acid reactive substances**

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CHAPTER 3

Bioactives and Pharmacology of *Cannabis sativa* L.

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3.1 INTRODUCTION

Cannabis sativa L. is a medicinal plant that belongs to the Cannabinaceae family (Merlin, 2003). The plant was recognized in various classical Ayurvedic texts, including *Vedas*, *Samhitas*, *Nighantus*, *Samgraha*, and *Granthas*. Many of these classical texts revealed the beneficial effect of this plant on various ailments. According to different Ayurvedic texts, several names have been employed to describe the findings based on the morphology and pharmacology of *Cannabis*. In relation to the cannabis plant, many synonyms have been attributed that are available in various Ayurvedic texts during different periods. The common name of Cannabis or *Vijaya* (Sanskrit) is *Bhanga* in Hindi and Cannabis in English, but along with this, approximately 40 synonyms ensure its availability that indicates their structure as well as therapeutic indications against different diseases. However, many synonyms also based on mythological origin demonstrate their close relationship with the society during the ancient period (Acharya et al., 2015).

As therapeutic activity against fever, diarrhea, urinary disorders, malabsorption syndrome, anemia, cough, tuberculosis, diarrhea with fever,

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inflammation, colic, meningitis, asthma, obesity, etc., Vijaya (*Bhanga*) have been observed for medicinal purpose (Acharya et al., 2015). Vijaya is used as a drug that was effective during the medieval period, which was used as an ingredient in the formulations which are basically available in different Ayurvedic compendiums. According to reports, about 191 formulations contain Vijaya as an ingredient, of which 187 formulations (internally), as well as 4 formulations (externally), exist in 13 different dosage forms. As an herbal product, *Cannabis sativa* L. was one of the earliest plants, used more than 10,000 years ago by human creatures. In the history of Cannabis, Hindus were among the first users, afterward, it was spread to Indo-Aryan culture outside India. Many people know today about Cannabis for psychological uses, but for many decades it was harvested predominantly for its fibers. Historical and archaeological findings demonstrate that the cannabis plant was employed in China since 4,000 B.C. for fibers, which further involved the manufacturing of ropes, textiles, strings, and even paper (Li, 1973). Regarding their medicinal importance, around 900 B.C. It was discovered as well as cultivated in India. In India, Cannabis use was broadly circulated as a medicinal and recreational drug. "Source of happiness," "Bringer of freedom," and "donator of Joy" are the words that signify the cannabis plant that was mentioned in the *Atharva Veda.* Therefore, this plant became part of numerous religious rituals in India (Touw, 1981).

In terms of their medicinal importance, this plant was used as an analgesic, anti-convulsant, hypnotic, tranquilizer, anti-inflammatory, anesthetic, anti-parasitic, antibiotic, diuretic, anti-spasmodic, antitussive, and expectorant (Touw, 1981; Mikuriya, 1969; Aldrich, 1997). In addition, Cannabis was traditionally used in Tibet, even though little bit of information has been written about its religious or medicinal use. In European culture, evidence revealed the availability of Cannabis before the Christian Era. In the year 450 B.C., Herodotus described a Scythian Funeral Ceremony and Stated that they inhaled the vapors in the form of aerosols from burning *Cannabis* seeds for euphoric and ritualistic purposes in Siberia and Germany. During the Initiation of the Christian Era (1000 A.D.), the Arabic nation mentioned the *Cannabis* plant in their texts as a digestive, diuretic, and anti-flatulent, 'to clean the brain' and to soothe the pain of the ears. Nearby in the 15th century, in Africa, Cannabis was used against snake bites, malaria, and fever, to promote delivery, blood poisoning, asthma, and anthrax, which spread to South America at the beginning of the 16th century. In the early 19th century, the effective importance of the Cannabis plant was revealed in western medicine through the works of Willian B. O'Shaughnessy, an Irish

Physician, and by Jacques-Joseph, a French Psychiatrist. However, as time passed, the western medical use of *Cannabis* significantly declined because of its limited efficacy during the first decades of the 20th Century (Zuardi, 2006). Along with India, Cannabis is produced commercially in Mexico and Africa. Commercially, it is mainly cultivated for fiber, oil, and psychoactive substances like charas, bhang, ganja, etc. (Kokate et al., 2009).

3.2 BIOACTIVES

C. sativa, which was used as a medicinal plant, contains approximately more than 450 chemical entities that signify almost all of the different biogenetic classes (Saroya, 2017). This section mainly demonstrates the main bioactive component with their structure. Attention has been focused on cannabinoids that represent the most important pharmacological activity of the *C. sativa* plant. Cannabinoids are chemical compounds with a C_{21} terphenophenolic skeleton isolated from the *C. sativa* plant. Together about 120 cannabinoids have been isolated to date from the initiation of constituent research that further sub-classified into 11 types, i.e., Δ^9-trans-tetrahydrocannabinol (Δ^9-THC), Δ^8-trans-tetrahydrocannabinol (Δ^8-THC), cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabinodiol (CBND), cannabielsoin (CBE), cannabicyclol (CBL), cannabinol (CBN), cannabitriol (CBT) and miscellaneous types. The structure of Δ^9-THC and their absolute configuration were freshly revealed by Gaoni and Mechoulam (1965).

Ahmed et al. (2008) isolated eight novel tetrahydrocannabinol types with their structure that was established on the basis of analytical instruments such as NMR and GC-MS. These compounds fragment into their two components to yield Δ^9-THC and the mono- or sesquiterpene under the high-temperature conditions of GC-MS. Δ^8-THC is another phytoconstituent of *C. sativa* with these three more compounds were also identified as 10α-hydroxy-Δ^8-tetra-hydrocannabinol, 10β-hydroxy-Δ^8-tetrahydrocannabinol, and 10aα-hydroxy-10-oxo-Δ^8-tetrahydrocannabinol. CBG was another pure-form chemical entity isolated from the resin of the Cannabis plant. Gaoni and Mechoulam (1965) described the CBC type that was further reported as sub-types namely, (±)-4-acetoxycannabichromene, (±)-3″-hydroxy-Δ^4″-Cannabichromene and (±)-7-hydroxycannabichromane. In accordance with Adams et al. (1940), CBD is found in other non-psychotropic (fiber-type) verities of *Cannabis sativa* plant in 1940 but their subtypes were investigated since 2005 that as mentioned by Elsohly and Slade (2005). These seven

CBD-type cannabinoids are namely cannabidiol (CBD), cannabidiolic acid (CBDA), cannabidiol monomethyl ether (CBGM), cannabidiol-C_4 (CBD-C_4), cannabidivarin (CBDV), cannabidivarinic acid (CBDVA), cannabidiocol-C_1 (CBD-C_1), cannabinodiol-C_5 (CBND-C_5), and cannabinodivarin-C_3 (CBND-C_3) are another two compounds that mainly represent the subclass CBND type that has been characterized in *C. sativa* (Elsohly and Slade, 2005).

Another cannabinoid sub-type is CBE type which further demonstrates five CBE types with an identical absolute configuration (5aS, 6S, 9R, 9aR) and named cannabielsoic acid A, CBE, cannabielsoic acid B, cannabielsoic acid B-C_3, and C_3-CBE. CBL, CBN, and CBT types were mentioned as the remaining cannabinoid type and CBL is the only representative that does not contain any further derivatives. In miscellaneous type, Elsohly, and Slade summarized some extra types including dehydrocannabifuran (DCBF-C_5), cannabifuran (CBF-C_5), 8-hydroxy-isohexahydrocannabivirin, cannabichromanone-C_5, cannabichromaone-C_3, 10-oxo-Δ tetrahydrocannabinol, etc. (Elsohly and Slade, 2005). Flavonoids as a bioactive component also possess great biosynthetic activity in Cannabis. Over 26 flavonoids have been isolated and detected in cannabis plants demonstrating seven chemical structures, i.e., vitexin, isovitexin, apigenin, luteolin, kaempferol, orientin, quercetin developed as methylated and prenylated aglycones or as O-glycosides or C-glycosides conjugate (Flores-Sanchez and Verpoorte, 2008). Stilbenoids are a small group of phenolic compounds identified in the *C. sativa* plant that is further divided into three main structural components, i.e., phenanthrenes, dihydrostilbenes, and spiroindans (Pollastro et al., 2018). In the roots, seeds, and fruits of the *Cannabis sativa* plant, mainly two groups such as phenolic amides and lignanamides were identified as lignans. Lignans represent a class of phenyl prostanoids whose carbon skeleton consists of the linking of C_6C_3 unit biosynthesized through the shikimate pathway. The structural representation of cannabinoids is depicted in Figure 3.1.

3.3 PHARMACOLOGY

The therapeutic properties of Cannabis have been studied since the mid-1990s. As a single entity, Cannabis contains over 60 different compounds collectively known as cannabinoids which are mainly responsible for the pharmacological activity of the plant. To initiate the biological response of cannabinoids, two separate cannabinoid receptors (CB1 and CB2) were cloned in 1990 and 1993, respectively (Zou and Kumar, 2018). Activation

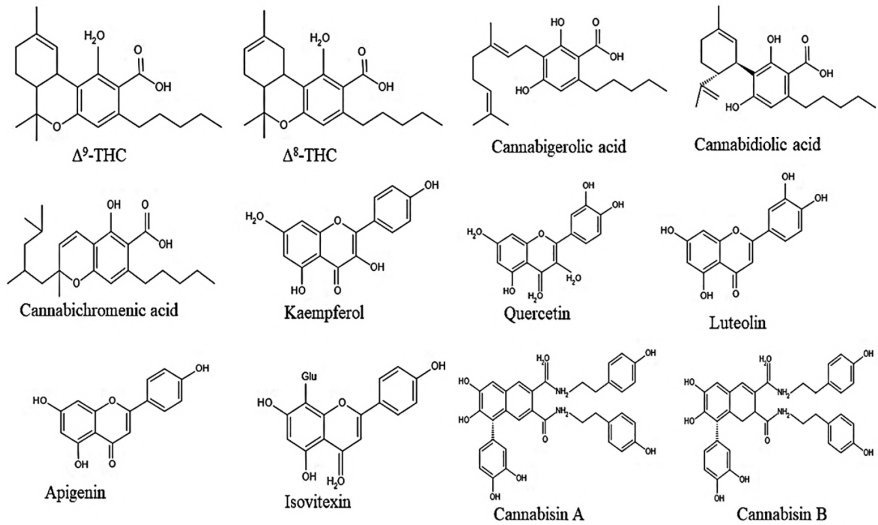


FIGURE 3.1 Chemical structures of phytoconstituents of *Cannabis sativa.*

of both receptors causes adenyl cyclase inhibition, decreased cAMP production, and modulation of ion channel activity via G-protein coupled receptor (GPCR). In terms of their location, CB1 receptors exist in high concentration in many tissue types throughout the body, including brain regions and the peripheral nervous system. However, CB2 receptors are more typically located on organs associated with the immune system (Kumar et al., 2001; Raymon and Walls, 2007).

The most active constituent found in *Cannabis sativa* is Δ^9-tetrahydrocannabinol (Δ^9-THC) (Wachtel, 2002) initially derived from hashish in 1964 by Gaoni and Mechloulam. Δ^9-THC is known for its significant activity against epilepsy, and analgesic properties in neuropathic and chronic pain. It mediates its psychoactive and allied physiological effects through GPCR, mainly CB_1R, and along with this effect, they also interact with CB_2R as well as non-CBR (Pertwee, 2006; Borgelt et al., 2013; Morales et al., 2017). In addition to Δ^9-THC, Cannabis synthesizes other cannabinoids, such as CBD, with an excellent pharmacological profile. Many neurological disorders such as psychosis, epilepsy, anxiety disorders, etc. (McGuire et al., 2017; Devinsky et al., 2018; Bergamaschi et al., 2011) are mainly regulated by CBD, which demonstrates its positive impact on brain dysregulation. Recently the United States Food and Drug Administration (USFDA) approved plant-based CBD against two rare genetic forms of

childhood epilepsy (Lennox-Gastaut and Dravet's syndrome) (O'Connell et al., 2017; Lattanzi et al., 2018).

Investigation of cannabinoids has still in process, and it is reasonable to assume that they also have good safety and tolerability profile. So, to highlight these aspects, chemovars were selected to identify a variety of cannabinoid profiles. Cannabichromene (CBC) has evolved as the third most abundant cannabinoid that affects transient potential profile (TRP) channels instead of CB_1 or CB_2 receptor (Morales et al., 2017; De Petrocellis et al., 2008). Cannabigerol (CBV) and CBDV were also found in chemovars extract with limited pharmacological profiles that mediate their limited actions through cannabinoid receptors (Morales et al., 2017).

For valuable information, a number of studies conducted that represent an increasing interest in the field of research. In addition to cannabinoids, non-cannabinoid bioactive compounds like propionamides and protein hydrolysates described some pharmacological potential that can be further explored (Lim et al., 2021). So, much more attention is required to highlight the beneficial effects of Cannabis. However, overconsumption of Cannabis has been negatively correlated with neurocognitive effects that may range from dilute attention, and dysregulation of learning and memory processes, to executive dysfunction which further limits cannabis use (Bloomfield et al., 2019). Withdrawal from chronic cannabis administration may decline dopaminergic transmission (Diana et al., 1998). Additional targets of CBD include 5-HT_{1A} receptors, α_1-adrenoceptors, and μ-opioid receptors (Pertwee, 2008). Reports from studies beyond non-human animals demonstrated that THC produces morphological changes in brain regions under the regulation of CB_1R. According to the data from the United States in 2012–2013, approximately 30.6% was the estimated percentage prevalence of cannabis use disorders (Hasin et al., 2015). A schematic representation of the endocannabinoid system that described the interaction of cannabinoids such as Δ^9-THC and other important constituents with their specific cannabinoid as well as the non-cannabinoid receptor is presented in Figure 3.2.

3.3.1 CENTRAL NERVOUS SYSTEM (CNS)

Chronic use of Cannabis is associated with psychological effects (Euphoria, dysphoria, anxiety, depersonalization), sedative effects (CNS depression, drowsiness, sleep, additive effect), cognitive effects (memory impairment, mental clouding, fragmentation of thoughts), and anticonvulsive activity (Gold, 1989). A recent report on Cannabis and its main active component

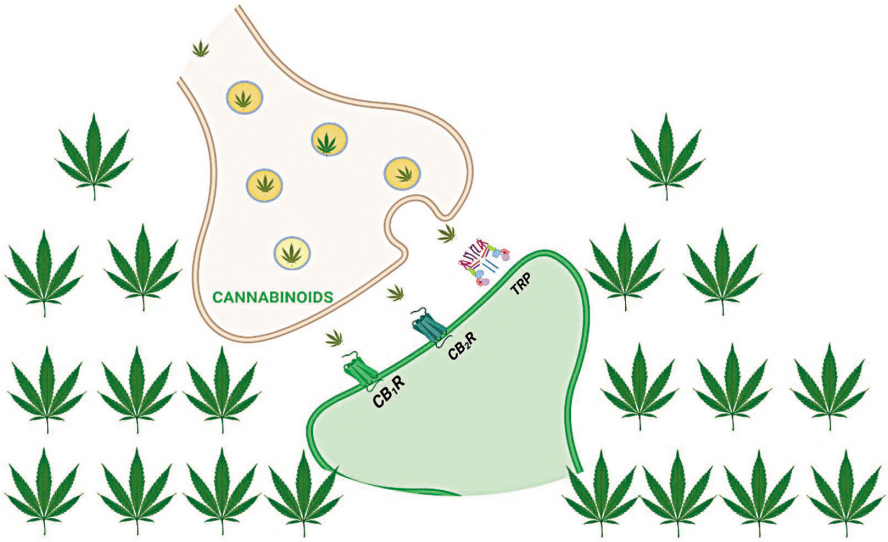


FIGURE 3.2 Representation of the endocannabinoid system that described the interaction of cannabinoids such as Δ^9-THC and other important constituents with their specific cannabinoid as well as a non-cannabinoid receptor.

Source: Drawn by author, created with BioRender.com.

exerts regulatory effects on the human brain. Researchers found a positive impact on obsessive-compulsive disorder patients (Kayser et al., 2020), however, other demonstrated psychotic symptoms exerted by Δ^9-THC (Colizzi et al., 2020).

3.3.2 CARDIOVASCULAR SYSTEM

Along with its evidence in CNS, endocannabinoids were detected in heart tissues that further regulate the heart rate and blood pressure. Evidence demonstrates the tachycardiac effect (up to 160 beats/min) with acute dosage, while bradycardia with chronic dose. A preclinical study indicates the vasodilatory effect in mice via activation of the CB1 receptor (Ashton and Ashton, 2001). As an important constituent of Cannabis, CBD exhibits beneficial effects in various health conditions, including the cardiovascular system. Studies showed vasodilation and antioxidant effects in hypertension. However, revealed no effect in hypertensive animals (Kicman and Toczek, 2020).

3.3.3 RESPIRATORY SYSTEM

Cannabis, especially Δ^9-THC revealed the bronchodilator property, anti-inflammatory, and antitussive activity in airways (Makwana et al., 2015). Chronic use of Cannabis increased symptoms of chronic bronchitis such as the production of sputum, coughing, and wheezing (Ribeiro and Ind, 2016) which may also lead to respiratory cancer on long-term administration (Aldington et al., 2008).

3.3.4 REPRODUCTIVE SYSTEM

On the basis of their pharmacological effect, CBD impact a negative effect on the reproductive system. These involve impairment of sexual behavior, reduction the testosterone secretions, impaired sperm production as well as disturbance of the ovulatory cycle. Moreover, a report from several studies revealed the negative effect of cannabis use in pregnancy because it can decrease birth weight (Carvalho et al., 2019). On the contrary, the effect of Cannabis on the evaluation of sexual functions of female health was conducted, and positive sexual effects in the domain of overall sexual satisfaction, orgasm, desire, and improvement in sexual pain have been reported. The United States of America has more than 22 million users of Cannabis which revealed its positive impact on sexual frequency in both men and women. Over 28,000 women and 22,000 men were analyzed to identify the positive association between cannabis use and sexual frequency (Sun and Eisenberg, 2017; Lynn et al., 2018).

3.3.5 ENDOCRINE SYSTEM

It was demonstrated that CBD may have an inhibitory effect on the endocrine system by regulating the function of the hypothalamus and pituitary gland. These include the inhibition of prolactin hormone through activation of the CB1 receptor on the pituitary gland, inhibition of growth hormone, and thyroid hormone by acting on the thyroid gland (Borowski et al., 2018).

3.4 CONCLUSION

C. sativa was described in various Ayurvedic texts. Its medicinal uses have been highlighted from the medieval period. Vijaya has been transformed into 191 formulations against several indications. It is produced commercially in Africa and Mexico along with India that was initially used as a psychoactive

substance which indicates the presence of Phyto-cannabinoids as a bioactive constituent. Its pharmacological response was studied since the mid-1990s after the discovery of cannabinoid receptors (CB1 and CB2), which demonstrate the efficacy to combat more than 29 disease conditions. So, Vijaya may be a good candidate against ailments, but there should be a need for more intensive scientific study to explore their indications.

KEYWORDS

- **cannabidiol**
- **cannabidiolic acid**
- **cannabidivarin**
- **cannabielsoin**
- ***Cannabis sativa***
- **marijuana**

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CHAPTER 4

Phytochemical and Pharmacological Appraisal of *Cassia angustifolia* Vahl. (Syn.: *Senna alexandrina* Mill.)

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4.1 INTRODUCTION

Cassia angustifolia Vahl. belongs to the Legumes family, Fabaceae. It is native to Yemen, Pakistan, Arabia, and Somalia. It is now cultivated in different countries of the world and is generally found growing in India (Tripathi, 1999). It is commonly known as Senna, Tinnevelly Senna, Rhubarb (English), Sanai (Hindi), Nela tangedu, Sunamukhi (Telugu), Nilavarai, Nelavakai (Tamil), Sunnamukki, Connamukki (Malayalam), Nela tangedu (Kannada) and Nat-ki-Sana (Gujarati).

Senna is a shrub, with a height of up to 1 meter, rarely it grows to two meters height. It is well branched with an erect stem and long spreading pale-green branches, leaves compound, paripinnate, leaflets 7–8 pairs, glabrous, yellowish green. Inflorescence raceme, flowers golden yellow in color. Fruit legume, flat, broadly oblong, horned, compressed, seeds six (Dongarwar et al., 2020).

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C. angustifolia is used as a medicament to treat splenic enlargements, anemia, typhoid, and cholera as a febrifuge, as a blood purifier, malarial, jaundice, as an anthelmintic, and as a remedy for constipation (Deshpande and Bhalsing, 2013). It has multifarious medicinal uses in Unani and other traditional medicinal systems. Traditional systems of Eastern and Western countries apply this plant mainly to treat constipation (Wallis, 2004; Balasankar et al., 2013) besides purgative, cathartic properties (Kisa et al., 1981; Chatterjee and Pakrashi, 1992; Tripathi, 1999; Dongarwar et al., 2020).

4.2 PHYTOCHEMICALS

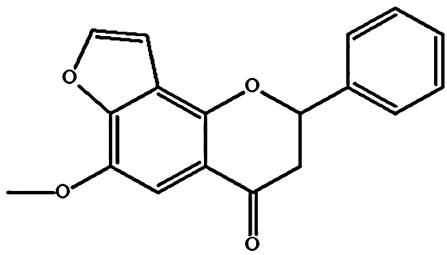
Naphthalene and tinnevellin-type glycosides were isolated from the leaves and pods of *C. angustifolia*. The structures of these constituents were established using spectroscopic methods (Lemli et al., 1981). Chemical constituents such as tinnevellin glycoside, isorhamnetin-3-*O*-beta-gentiobioside, apigenin-6,8-di-C-glycoside, emodin-8-*O*-beta-D-glucopyranoside, kaempferol, aloe emodin, D-3-*O*-methylinositol, sucrose was isolated from leaves of *C. angustifolia* (Wu et al., 2007).

Sennosides are the main constituents in the leaves and pods of this plant. The concentration of sennosides (A and B) in the natural drug decides the quality, acceptability, and price in the market (Oshio et al., 1978). These components are regarded as chief components amenable to the purgative properties (Kisa et al., 1981). Therapeutically active constituents of the senna extract are the anthraquinones, in addition to the senna-specific dianthrones, called sennosides. Sennosides and other glucosides act as pro-drugs for the laxatives such as anthrones and anthraquinones (Lemli, 1988). Sennosides are metabolized by the intestinal bacteria to rhein-anthrone which acts in the intestine as a direct purgative (Yang et al., 1996). Sennosides are listed as one of the most important pharmaceutical preparations of plant origin (Morinaga et al., 2000). Ratnayaka et al. (2002) studied the effect of nitrogen concentration on the Sennosides contents in leaves and reported that the youngest leaves showed a high yield. Wu et al. (2009) reported kaempferol-3-*O*-[(6‴-*O*-trans-sinnapoyl)-β-D-glucopyranosyl (1→6)]-β-D-glucopyranoside and apigenin-6,8-di-C-glycoside as new flavonoids from the leaves of *C. angustifolia*.

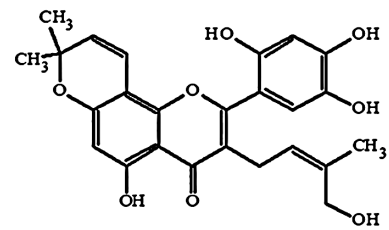
The presence of anthraquinone glycosides, namely sennoside A–D and different types of glycosides, flavonoid (kaempferol), anthrone diglucoside, and naphthalene glycosides such as tinnevellin glycoside and 6-hydroxy musizin glycoside, phytosterols, resin, and calcium oxalate have been reported (Kokate et al., 2003; Agarwal and Bajpai, 2010). Rosenthal et al.

(2014) have introduced a method for the estimation of Sennosides based on the photometric methods and validated the sennoside A and B using HPLC.

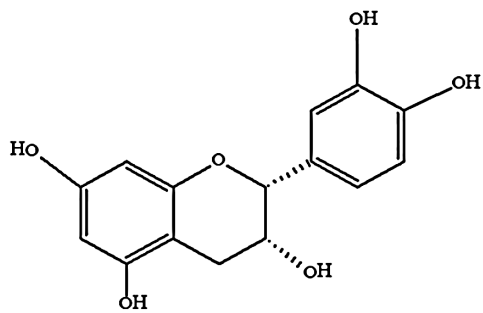
Qualitative phytochemical analysis results revealed the presence of different types of phytoconstituents such as phenolic groups (phenols, flavonoids, tannins), resins, saponins, steroids, and alkaloids from *Senna* leaves, flowers, and pods extracts obtained from various solvent systems (Kistamma et al., 2014). The extraction and HPLC separation as well as quantification of madagascine (3-isopentenyloxyemodin) and 3-geranyloxyemodine from dried leaves and fruits of *C. angustifolia* (Syn.: *Senna alexandrina)*, were determined. In addition, the effective chemical and analytical methodologies to detect in a single chromatographic run typical anthranoids components such as emodin, physcione, aloe-emodin, rhein, and chrysophanol.



(-)-(2S)-6-Methoxy-[2",3":7,8]-furanoflavanone



14-Hydroxyartonin *E*

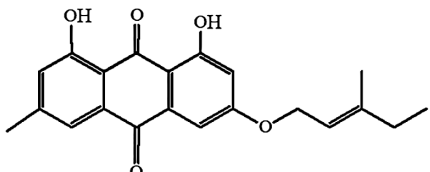


(−)-epicatechin

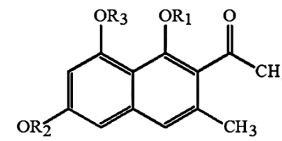
The quantification of madagascine and 3-geranyloxyemodin in the leaves and pods was established by using HPLC (high-performance liquid chromatography) which are unprenylated anthranoids that are commonly found in *C. angustifolia* as well as from *Aloe vera* (Epifano et al., 2015). Shahina et al. (2016) investigated the methanolic extract of leaves and reported the volatile constituents such as 1 butanol, 3 methyl acetate, 6,6-dideutero-nonen-1-ol-3,

pentadecanoic acid, squalene, and Vitamin E identified by gas chromatography coupled with mass spectrum.

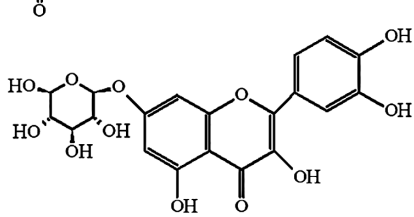
A series of monoanthrones was shown to be present in smaller amounts in addition to aloe, mono-, and diglucosides (aloe-emodin-dianthrone diglycoside, aloe-emodin-8-glucoside, aloe-emodin-anthrone-diglucoside) from the leaves (Ramchander et al., 2017). Further, Dhanani et al. (2017) determined the quantification method for a yield of sennoside A and B using conventional and non-conventional processes and validated the HPLC-PDA detection method more effectively.



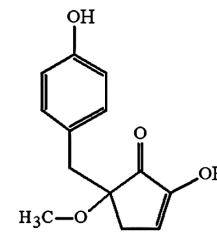
1: Madagascine
2: 3-Geranyloxyemodine



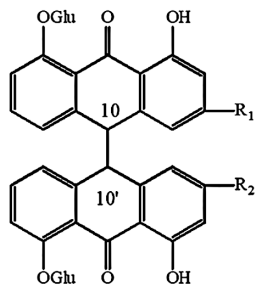
6-Hydroxymusizin Glucoside
R1, R2 =H; R3=b-Glucopyranosyl
Tinnevellin Glucoside
R1=H; R2=b-Glucopyranosyl; R3=CH3



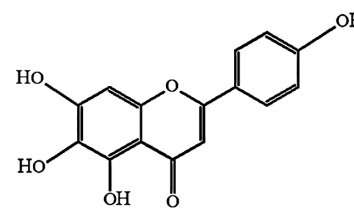
Quercimeritrin



Vidalenolone



Sennoside B (R1/R2:COOH; 10-10' MESO)
Sennoside A (R1/R2:COOH; 10-10' TRANS)



Scutellarin

Tushar et al. (2017) calculated and evaluated the yield and composition of the extract of senna using cold percolation at room temperature and refluxing (conventional) and ultrasound and microwave-assisted solvent extraction (SE) as well as supercritical fluid extraction (SFE) (non-conventional) high throughput methods. In addition, a rapid reverse-phase HPLC-PDA detection technology has been developed and validated for the determination of sennoside A and B in the extracts of senna leaves. It is also found that the Ultrasound and microwave-assisted SE techniques were proved as effective, and the metabolites of the extracts were compared to cold percolation at room temperature and refluxing methods of extraction. In addition, the senna also possesses amino acids, alkaloids, flavonoids, carbohydrates, and tannins. Khare et al. (2017) reported the analytics such as ash value and acid soluble or insoluble components and the total extractive values from the aqueous and organic solvents. The phytoconstituents namely, N-(methyleneamino)-2, 4-dinitroaniline; Tricyclo[5.1.0.0(2,8)]oct-4-en; Tricyclo [5.1.0.0(2,8)] oct-3-en; 3-diazoacetyl-4-methoxy carbonylpyridiine, Trichlorocyclopentane, Nitrophenyl azide, and undecane were characterized from the leaves using GC-MS studies of ether soluble substances (Hemadrireddy et al., 2018). The extracts were obtained in different methods such as Microwave, Soxhlet, Sonication, Marinated, and Reflux extractions and subjected to HPLC and MS studies and identified the active flavonoids like epicatechin, (–)-(2S)-6-methoxy-[2″,3″:7,8]-furanoflavanone, kaempferol 3-O-sulfate-7-O-c-arabinopyranoside, Vidalenolone, (2*S*)-7,8, bis-3′,4′-(2,2-dimethylchromano) – 5-hydroxyflavanone 3,7-dihydroxy-4,' 8-dimethoxyflavone, and 14-hydroxyartonin *E* (Laghari et al., 2011).

4.3 PHARMACOLOGY

4.3.1 ANTIMICROBIAL ACTIVITY

Water extracts and nanoparticles synthesized from *C. angustifolia* were evaluated for antimicrobial activity against *Staphylococcus aureus* and *E. coli*, revealing that nanoparticles were highly effective on *S. aureus* (Peter et al., 2012). The methanol extract of *C. angustifolia* leaves was reported for a significant and broad spectrum of effects against pathogenic bacterial strains such as *Klebsiella pneumoniae*, *E. coli*, and *Shigella shinga* (Bameri et al., 2013). The antimicrobial effect of methanol and ethanol extracts of *C. angustifolia* on pathogenic bacteria was determined using the broth

micro-dilution method. The result shows that the MIC value of leaf methanol extract exhibited stronger activity against *K. pneumoniae* with MIC: 0.62 mg/ml (Zakaria et al., 2013).

The leaf extracts of the medicinal plant *C. angustifolia* exhibited significant inhibition against *E. coli* (gram-negative) and *S. aureus* (gram-positive). The solvent extracts like acetone, methanol, and water obtained from *C. angustifolia* were grown in three different soils such as normal soil, soils treated with heavy metals, and soils treated with calcium hydroxide along with heavy metals. Gram-positive bacteria, *S. aureus* was strongly inhibited by all the tested extracts obtained from three different treated soils than *E. coli* (Singanboina et al., 2014).

The extracts of *C. angustifolia* showed variable degrees of antibacterial activity against the tested pathogens. It showed that methanol extract strongly inhibited the selected bacterial stains *in vitro* conditions. The ethyl acetate (EA) extract exhibited the highest bactericidal activity against *Serratia marcescens.* Water extract failed to inhibit *Acinetobacter junii*, *E. cloacae,* and *Pseudomonas aeruginosa*. *S. marcescens* was strongly inhibited by ethanol extract, but no effect was observed against *E. faecalis* and *P. aeruginosa*. Whereas *A. junii, S. marcescens, E. cloacae,* and *Sa. typhi* were sensitive to acetone extract (Ahmed et al., 2016).

The extract exhibited a significant broad spectrum of antibacterial activity on the tested gram-positive bacteria such as *S. aureus, Streptococcus mutans, Lactobacillus casei, L. acidophilus, Bacillus megaterium* and gram-negative organisms *Enterococcus faecalis, Xanthomonas campestris, E. coli* and *Pseudomonas aeruginosa.* Among the tested extracts the methanol fraction is highly significant than the hexane (Vijayasekhar et al., 2016). The EA extract of leaves was effective against the plant pathogenic bacteria such as *Pseudomonas fuscovaginae, Erwinia chrysanthemi,* and *X. oryzae* pv. *oryzae* (Premalatha and Lakshmi, 2020).

4.3.2 ANTIFUNGAL ACTIVITY

A new triterpenoid glycoside isolated from *C. angustifolia* seed butanolic extracts. Its structure was elucidated as 3-*O*-{β-D-glucuronopyranosyl-(1→4)-[β-D-galactopyranosyl-(1→2)]-β-D-xylopyranosyl-(1→3)–β-D-glucopyranosyl}-2, 16α-dihydroxy-4, 20-hydroxy methyl olean-12-ene-28-oic acid on the basis of spectral studies evaluated for its antifungal activity and found effective on *Colletotrichium dematium* (Khan

and Srivastava, 2009). The extracts and isolated constituents such as quercimeritrin, scutellarein, and rutin of *C. angustifolia* proved as significant anticandidal agents in the *Candida albicans* (Ahmed et al., 2016). The extracts of *C. angustifolia* showed antifungal activity against *C. rugosa, C. albicans, Aspergillus niger,* and *Rhizopus oryzae,* and methanol extract proved to more effective on *C. rugosa* whereas hexane extract showed the least effect (Vijayasekhar et al., 2016).

4.3.3 THE LAXATIVE EFFECT

The mechanism of action for the laxative activity is well-known and consists of stimulation of colonic peristalsis by the release of endogenous substances (autacoids, nitric oxide (NO)) and by altering the absorption and the secretion of water and electrolytes into the colon's lumen, owing to the inhibition of Na^+/K^+-adenosine triphosphatase (Capasso et al., 1983). This effect and acute toxicity of a few fractions of *C. angustifolia* extracts in mice with several pure anthraquinone derivatives of pods showed the laxative and toxic components. The mixture of sennoside A and B fractions was identified as the most effective laxative molecules and were evaluated as least toxic whereas the rhein-8-glucoside-rich fraction showed acute toxicity. It is also proved that the interaction of rheinanthrone with immune cells of the colon has the laxative property (Hietala et al., 1987; Lemli, 1995).

4.3.4 ANTIDIABETIC ACTIVITY

Shravankumar et al. (2015) reported a significant effect on the activity of carbohydrate metabolizing enzymes such as α-amylase and α-glucosidase *in vitro* system. Methanolic extract of *C. angustifolia* leaves showed a significant antihyperglycemic effect on the alloxan-induced diabetic mice along with a gain in body weight (Hemadrireddy et al., 2017). The antidiabetic activity of hydroalcoholic extract of leaves was found effective in controlling glucose tolerant test at the dose of 400 and 800 mg/kg BW. The extracts showed a significant antidiabetic effect in streptozotocin (STZ) induced female Sprague-Dawley rats. The extract (800 mg/kg BW) exhibited a significant decrease in glucose and enhanced insulin in the serum of the 21-day treated rats. In addition, the extract also affected the total cholesterol level and altered the HOMA-IR or atherogenic indices. There is no change in the creatinine level. The histopathological evidence supports the recovery

of beta cells of the pancreas in the treated rats indicating the significant role in the management of diabetes (Jani and Goswami, 2020).

4.3.5 HEPATOPROTECTIVE ROLE

The alcoholic extract of the leaf demonstrated a protective role on CCl_4-induced liver toxicity in mice evaluated the serum biochemical markers such as proteins, bilirubin, GPT (glutamate pyruvate transaminase), GSH (glutathione) and GOT (glutamate oxaloacetate transaminase) and LPO (lipid peroxides) along with histopathological studies demonstrated as a potent hepatoprotective natural medicament (Ilavarasan et al., 2001). The detailed biochemical and histopathological studies *in vitro* and *in vivo* indicated the safety usage of senna in humans (Vitalone et al., 2011).

4.3.6 ANTIOXIDANT ACTIVITY

The leaves and flowers were phytochemically evaluated for the antioxidant studies using DPPH scavenging properties (Ahmed et al., 2016).

The methanol fraction obtained from leaf extract of *C. angustifolia* (MEFCA) tested on carbon tetrachloride (CCl_4) induced hepatotoxic adult rats and found significant downfall observed in CCl_4 induced elevated levels of hepatic markers such as total cholesterol, triglycerides, and low-density lipoprotein and enhanced high-density lipoprotein compared to the CCl_4 group. Moreover, pre-treatment with the MEFCA produced significant reductions in lipid peroxidation (LPO) and protein carbonyl levels in liver tissues as compared with the untreated group. The leaf extract strongly prevented the formation of pathological hepatic lesions (Bellassoued et al., 2019). Premalatha and Lakshmi (2020) reported radical scavenging (ABTS) activity, inhibition of LPO, superoxide radical scavenging activity, NO radical scavenging activity, and metal chelating activity as a part of *in vitro* antioxidant studies.

4.3.7 ANTICONVULSANT EFFECT

The anticonvulsant effect (anti-epileptic) of ethanolic extract of seeds of *C. angustifolia* using maximal electroshock (MES) and pentylenetetrazole (PTZ) induced seizures in rats with the dosage of 100, 200, and 400, mg/kg.

p.o. The onset and duration of Hind Limb Tonic Extension were noted and the ethanolic seed extract significantly abolished the hind limb tonic extension with the 400 mg/kg dose is reported as more significant and protected the animals from induced tonic convulsions. This may affect through Gabergic inhibitory and glutaminergic excitatory mechanisms or inhibition of the voltage-gated sodium channel (Shravan et al., 2016).

4.3.8 ANTICANCER ACTIVITY

The bioactivity-guided separation of *C. angustifolia* extracts, resulted in three flavonoids quercimeritrin, scutellarein, and rutin which showed significant anticancer activity against MCF-7 (IC_{50}, 4.0 μg/μl), HeLa (IC_{50}, 5.45 μg/μl), Hep2 (IC_{50}, 7.28 μg/μl), with low cytotoxicity against normal HCEC (noncancerous cell line) with the IC_{50} of 21.09 μg/μl by the MTT colorimetric assay (Ahmed et al., 2016).

Long-term use of sennoside reported to induce the disease of the skin coli (Melanosis Coli) and probably will increase large intestine cancer risk. Sennosides alter colonic sculpture length, proliferative activity, and bcl-2 expression 18 h when administration. The results of acute sennoside use and therefore the presence of megacycle on large intestine animal tissue were studied on 15 subjects receiving sennosides for 6 h and were analyzed for degree of necrobiosis (H&E staining), immunohistochemical p53, p21/WAF and bcl-2 expression, and proliferative activity. They supported the molecular marker studies p53 expression or bcl-2 expression or LI and different cancer-connected markers, sennosides acutely induce necrobiosis of colonic animal tissue cells, presumptively by a p53, p21/WAF-mediated pathway, leading to shorter crypts. Moreover, the sennosides provided protecting tendency throughout severe disease of the skin coli, delayed necrobiosis, or apoptosis inflicting longer crypts while not an increase in proliferative activity or bcl-2 expression (van Gorkom et al., 2001).

4.3.9 IMMUNOMODULATORY EFFECTS

In cyclophosphamide-induced immunosuppressed male Swiss albino mice, the methanolic leaf extract of *C. angustifolia* was given orally at doses of 2, 5, and 10 mg/kg BW for 14 days. In animals, oral treatment of the extract caused leucocytosis, which was followed by a considerable rise in neutrophil counts in a dose-dependent manner. The “neutrophil phagocytic

index" and "delayed-type hypersensitivity reaction" improved, according to the findings. At a dosage of 5 mg/kg BW, the immunological responses were determined to be the strongest. In immuno-compromised animals, the values for hemagglutination antibody titer increased in a dose-dependent manner, indicating that the extract had a stimulatory impact on both cell-mediated and humoral immune responses (Akshay et al., 2019).

4.3.10 ANTIMUTAGENIC ACTIVITY

The ethanol extract of *C. angustifolia* (CAE) was evaluated for the genotoxic and agent effects of inactivation of *E. coli* cultures; microorganism growth inhibition; reverse mutation check (Mutoxi-test) and polymer strand break analysis in inclusion body polymer. The extracts alone demonstrated as noncytotoxic to tested *E. coli* strains. Whereas the CAE was ready to defend itself from H_2O_2-induced toxicity in *E. coli* IC203 (uvrA, oxyR) and IC205 (uvrA, mutM) strains, inferring its inhibitor/antimutagenic action (Silva et al., 2008).

4.3.11 RADIO PROTECTION STUDIES

The cytology (micronucleus and chromosomal abnormality study) and its effects of calcium sennosides at an operating dose (24 or 48 mg/ml) were reported for suppressing radiation hazards in human blood cultures. The radiation exposure induced an important increase in micronuclei (MN) frequencies in each mono- and bi-cell organ cell, and chromosomal aberrations, besides decreased levels in SOD (superoxide dismutase) and CAT (catalase). Whereas, IL-8, cyclooxygenase, and LDH levels were considerably enhanced after irradiation were significant. The treatment with calcium sennosides showed weakened MN and chromosomal aberration numbers and the level of SOD and CAT activities. In addition, a strategic recovery in IL-8, TNF-α, cyclooxygenase (LOX) levels, and LDH activity disclosed the antimutagenic and the medicinal capacity of sennosides on the oxidative stress ignited by γ-irradiation (Ahmed et al., 2018).

4.3.12 BIOTRANSFORMATION OF SENNOSIDES IN BOWEL

An immunochemical assay for the quantitation of nanogram amounts of sennoside B and connected compounds in plant extracts is delineated. The

assay is applied to the analysis of sennoside formation and distribution in *C. angustifolia*. High levels of sennosides in dried leaves and fruits are determined whereas the seeds, stems, and roots contain little sennoside. The flowers were reported for 4–5% of sennoside B in its dry weight in addition to the immunomodulating constituents. Besides, it also reported that a three-day seeding cotyledon also possesses sennoside B at an equal level as a leaf. Upon dehydration, leaf levels of sennoside B rise steadily, this rise being reciprocally correlated with the water loss. Absolutely the levels of sennoside B fashioned in this manner square measure similar as compared to fast drying at 60°C (Atzorn et al., 1981). Intra-caecal administration of rheinanthrone, the intraluminally active matter of sennosides A and B, to mice quickly induced severe diarrhea. Pre-treatment with the autacoid (PG) synthesis substance, nonsteroidal anti-inflammatory, and PGE2 antagonist (SC-19220), prevented the onset of diarrhea induced by rheinanthrone (the active ingredient of *C. angustifolia*), however, the PGE2 antagonist polyphoretin phosphate (PPP) showed solely a weak restrictive result. Rheinanthrone excited the assembly of PGE-like material solely within the colon and its giant enteral propulsive activity was depressed by nonsteroidal anti-inflammatory and SC-19220, however, not by palate-pharyngoplasty that suggests that the discharge of PGE-like material has some role in its purgative action (Yagi et al., 1988).

Laxative effects of shrub preparations square measure primarily mediate by rheinanthrone, a matter fashioned within the microorganism from dianthrones. Notwithstanding, it absolutely was not clear whether or not dianthrones square measure bioavailable in the least and contribute to the effects of this vital medicative plant. Mistreatment of the Caco-2 human colonic cell line as an *in vitro* model of the human enteral tissue layer barrier, the bioavailability of dianthrones was studied in the top to basolateral (absorptive) and basolateral to top (secretive) direction. Porousness coefficients ([P.sub.c]) and percent transport were calculated supported quantifications by HPLC. Sennosides A and B, and their aglycones sennidine A and B square measure transported through the Caco-2 monolayers in a concentration-dependent manner and their transport was linear with time. The absorption in the top to basolateral direction was poor and [P.sub.c] values were similar to a diuretic drug. The transport was higher within the body fluid direction, indicating a big effluence (e.g., by effluence pumps) of the (poorly) absorbed compounds within the enteral lumen once more. The findings on the natural laxative effect of dianthrones have been explored by Waltenberger et al. (2008).

4.3.13 PORTAL VEIN THROMBOSIS

In a case study, A 42-year-old lady suffered from a five-day history of worsening epigastric pain, anorexia, episodic expulsion, and intermittent fever. She intimated that she had stewed dried shrub leaves that were bought from herbalists and drank about 200 milliliters daily for two-years. Color Doppler screening found the echogenic clot destructed the portal vein and bifurcation and seizure of blood flow. Treatment with thrombolytics was unsuccessful. Severe hepatotoxicity shrub use is uncommon. Soyuncu et al. (2008) opined that the explanation for senna-related hepatotoxicity is unclear however can be explained by the exposure of the liver to uncommon amounts of ototoxic metabolites of anthraquinone glycosides. Chronic use of shrubs might seldom be related to portal vein damage.

4.3.14 CLINICAL KNOWLEDGE OF SAFETY

Quality clinical trials evaluating the effectiveness and safety of shrubs within the treatment of constipation, still as comparative trials comparing shrubs with different laxatives, a square measure typically lacking. However, a 2014 double-blind, randomized, active-comparator trial found 2 capsules daily for six days as effective as lubiprostone (Amitiza) for rising constipation-related symptoms and quality of life in adults UN agency skilled opioid-induced constipation following orthopedical surgery. Widespread use of shrubs and older clinical studies have a light-emitting diode to the acceptance of shrubs as an efficient laxative in adult populations for the treatment of chronic constipation, constipation because of different medicines (such as opioids), and in making ready the gut for diagnostic procedures, though various laxatives are also safer and simpler (Ramkumar and Rao, 2005; Ulbricht et al., 2011; Candy et al., 2011; Gordon et al., 2012; Marciniak et al., 2014).

4.3.15 SIGNALING ROLE IN PHARMACOLOGIC EFFECTS

Rhein could be a major medicative ingredient isolated from *C. angustifolia* which has various pharmacologic effects such as antioxidant, antitumor, hepatoprotective, antifibrosis, and nephroprotective activities. The mechanism of rhine involves multiple pathways with close interactions. The targets of rhine, square measure initiated by the membrane receptor resulting in activating the MAPK and PI3K-AKT parallel signaling pathways, and a

number of other downstream pathways were being affected, thereby eventually involving the regulation cell cycle and programed cell death. The therapeutic result of the rhine, as a multitarget molecule, is that the synergistic and comprehensive results of the involvement of multiple pathways instead of the block or activation of one signaling pathway (Sun et al., 2016).

4.4 CONCLUSION

The extracts of senna were presumably utilized as a laxative along with many beneficial biological effects in the human with the least side effects except its long-term usage in high dosages. This herb is also being cultivated in many countries and is widely popularized. The usage of senna is also appreciated in traditional medicinal systems and modern techniques are supported its medicinal claims when used systematically.

KEYWORDS

- ***Cassia angustifolia***
- **legumes**
- **pentylenetetrazole**
- **pharmacology**
- **senna**
- **super oxide dismutase**

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CHAPTER 5

The Genus *Atalantia*: A Comprehensive Review of Phytoconstituents, Ethnobotany, and Pharmacological Bioactivities

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5.1 INTRO DUCTION

Genus *Atalantia* belongs to the family Rutaceae. It represents about 17 flowering plant species, native to the tropics and subtropical regions of Asia (Huang, 1997). Among them about 11 species distributed from Peninsular Malaya, Thailand, Myanmar, Vietnam, India, Andaman, Nicobar Islands, Laos, Cambodia, South China, Sumatra, Sri Lanka, and Java (Swingle and Reece, 1967). India is represented by only five species, which are *A. simplicifolia* (Roxb.) Engl. (Syn. *Amyris simplicifolia* Roxb., *A. caudata* Hook.f., *A. roxburghii* Oliv., *Sclerostylis roxburghiana* Hook.f. and Thomson, *Sclerostylis roxburghii* Wight) distributed from Northeast India (Assam, Meghalaya, Mizoram, and Nagaland) and Nicobar Islands. *A. wightii* Tanaka (Syn. *A. ovalifolia* Yu.Tanaka) from Western Ghats. *A. racemosa* Wight [Syn. *A. capitellata* Lindl., *A. disticha* (Blanco) Merr., *A. racemosa* var. *bourdillonii* K. Narayanan and M. P. Nayar, *A. nitida* (Turcz.) Oliv., *A. parvifolia* M. Roem., *Lampetia racemosa* M. Roem., *Limonia disticha* Blanco, *Sclerostylis nitida* Turcz., *S. ovalifolia* Wight, *S. parvifolia* Wight, *S. racemosa* Wight, *Severinia disticha* (Blanco)

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Swingle] and *A. monophylla* (L.) DC. [Syn. *Trichilia spinosa* Willd., *A. carissoides* Wall., *A. floribunda* Wight, *A. malabarica* (Raf.) Yu.Tanaka, *A. platystigma* Wight, *A. puberula* Miq., *A. spinosa* (Willd.) Yu.Tanaka, *A. umbellata* M.Roem., *Limonia spinosa* Spreng.] are wildly distributed from the Western and Eastern Ghats of peninsular India (Ranade et al., 2009). *A. ceylanica* (Arn.) Oliv. [Syn. *Limonia citrifolia* Moon, *L. monophylla* L., *Rissoa ceylanica* Arn., *S. arnottiana* Wight, *S. ceylanica* Wight, *S. zeylanica* Hook.f.] is widely distributed from India, Sri Lanka, and Vietnam (Anonymous, 2021a). Along with Indian species, *A. buxifolia*, commonly known as Chinese Boxorange, is distributed from China, Hainan, Malaysia, Laos, Philippines, Taiwan, and Vietnam (Zhang et al., 2008; Anonymous, 2021b). *A. retusa* [Syn. *Severinia retusa* (Merr.) Swingle], locally known as Tulan Manok and endemic to the Philippines (Raga et al., 2010; Anonymous, 2021c). *A. sessiliflora* Guillaumin is native to Vietnam (Le et al., 2020; Anonymous, 2021d). *A. roxburghiana* Hook.f. (Syn. *Sclerostylis amyridoides* M.Roem.) is native from Bangladesh, Malaya, and Vietnam (Rashid et al., 1995; Anonymous, 2021e). *A. guillauminii* Swingle is native to China and Vietnam (Huang, 1997; Anonymous, 2021f). Genus resembles *Citrus* trees, with fragrant white flowers and globose fruits like limes or oranges (The Wealth of India, 2000).

Plants of *Atalantia* are shrubs or small armed trees. Leaves 1-foliate, elliptic. Flowers crowded, axillary fascicles, racemose or corymbose cyme, contracted or elongated, fragrant. Calyx regularly or irregularly lobed with 3–5, rounded or subacute lobes, ciliate, split to the base on one side. Petals white, broadly elliptic or obovate or concave, glandular. Stamens 8, disc cupular, connate into a tube or free, filaments united into a tube almost throughout their entire length. Ovary ovoid, oblong or obovoid, sunk in the disk. Style short, stout, and clavate. Stigma clavate. Fruit berry, globular, 1–5 seeded.

Plants from the genus are used to treat Kapha, Vata, flatulence, colic, hemiplegia, arthritis, skin diseases, bacterial infections, and malignancy. Acridone alkaloids reported from the genus have several biological activities such as induction of human promyelocytic leukemia cell (HL-60) differentiation (Kawaii et al., 1999a), and antiproliferative activity (Kawaii et al., 1999b). Silver nanoparticles from methanolic leaf extract of *A. monophyla* had potential antimicrobial activity against pathogenic microorganisms (Mahadevan et al., 2017). Berry, root, leaf, fruit, and seeds of *A. monophylla* are used to treat fever, paralysis, chronic rheumatism, abdominal disorders, skin eruptions, asthma vomiting, cough, traumatic injury, stomach-ache, hernia, indigestion, snakebite poisoning and also used as an antiseptic,

antispasmodic, and stimulant (Basa, 1975; Panda, 2004; Munuswamy et al., 2016). For itching and other skin, complaints leaves decoction is used (Panda, 2004). For rheumatoid pain and glandular swelling treatments, boiled leaves are used (Sankaranarayanan et al., 2010). Pulayar tribes from the Thadagai hills of India used it's leaves to treat swellings (Thirugnanasampandan et al., 2015). Malayali tribal community from Jawadhu hills of Tami Nadu, India, used a decoction of the leaves against itching and other cutaneous complaints (Ranganathan et al., 2012). A person suffering from rheumatism, berry oil and stem as a hand stick are also found effective (Prusti and Behera, 2007; Murthy, 2012). In the Villupuram district of Tamil Nadu, India, essential oil is isolated from the fruits and used to get relief from joint pain (Sankaranarayanan et al., 2010). Roots are traditionally used as an antispasmodic (Kirtikar and Basu, 1999). Malayali tribal community from Jawadhu hills of Tami Nadu, India used roots for treating rheumatism and swelling (Ranganathan et al., 2012). *A. monophylla* possess antifungal, antioxidant, anti-allergic, antihepatotoxic, stimulant, antispasmodic, anti-inflammatory, antimalarial, antimicrobial, antiviral, cytotoxic, antifeedant, and insecticidal properties (Luthria et al., 1989; Baskar et al., 2009, 2012; Reddy et al., 2010). Plants from the genus are also used in the treatment of paralysis, snakebite, and chronic rheumatism (Govindachari et al., 1970; The Wealth of India, 2000; Kumar et al., 2009). *A. racemosa* is commonly known as Kattu Naragam and used in chronic rheumatism, itching skin, blood purification, paralysis, herbal formulation, asthma, bronchitis, cough, fever, allergy, and acidity (Sukumaran and Raj, 2010; Luthria et al., 1989; Pullaiah, 2006; Harsha et al., 2002). *A. buxifolia* has been used in the treatment of paralysis, snakebites, cough, sputum, traumatic swelling, pain, rheumatism, and malaria (Gu and Han, 1986; Wu and Chen, 2000; Yang et al., 2012a). *A. ceylanica* is commonly known as Yakinaran. Leaves are used against catarrh, bronchitis, influenza, liver diseases, and other chest complaints (Jayaweera, 1982; Dassanayake and Forsberg, 1985; Munasinghe et al., 2015). *A. retusa* is also used to treat various ailments (Raga et al., 2010). *A. roxburghiana* leaves and fruits are locally used for the treatment of respiratory problems, stomach upset, rheumatism, and tumor (Rashid et al., 1995).

5.2 BIOACTIVES

A number of researchers reported steroids, acridone alkaloids, terpenoids, and coumarins from this important genus (Basa, 1975; Govindachari et al., 1970; Kulkarni and Sabata, 1981; Sabata et al., 1977). Joshi et al. (2011);

and Premalatha and Karthi (2017) reported alkaloids, flavonoids, tannins, steroids, saponins, carbohydrates, cardiac glycosides, terpenoids, phenols, and proteins from leaves and roots of *A. monophylla*. *A. monophylla* roots contain a number of acridone alkaloids and limonoids. For the first time, Thakar and Sabata (1969) isolated the limonoid, atalantin from the root petrol extract. Further, Govindachari et al. (1970) isolated two new acridone alkaloids namely atalaphylline and N-methylatalaphylline. Similarly, Talagatra et al. (1970) reported another acridone alkaloid called xanthyletin. Basu and Basa (1972) and Auzi et al. (1996) reported a new acridone alkaloid, N-methylbicycloatalaphylline from the petrol extract of the dried roots. Basa (1975) reported acridone base atalaphyllinine in trace amounts from the root. Dreyer et al. (1976) isolated and revised structures of three known limonoids *viz*. atalantin, dehydroatalantin, and cycloepiatalantin from the root bark of *A. monophylla*. Sabata et al. (1977) also revised the structures of two limonoids (atalantolide and atalantin) isolated from the root bark. The structure of severine palmitate from *A. monophylla* was revised and confirmed using ^{13}C NMR (Dreyer et al., 1980). Minor acridone alkaloid, atalaphylline 3,5-dimethyl ether has been isolated from the root bark of *A. monophylla* (Kulkarni and Sabata, 1981). Further, N-methylataphyllinine, yukocitrine, and junosine were also reported (Auzi et al., 1996). In addition, citrusinine-I, buxifoliadine-A, buxifoliadine-E, auraptene, and 7-O-geranylscopoletin were also reported (Kawaii et al., 1999a; Wu et al., 2001; Wu and Chen, 2000; Jiménez et al., 2000; Iranshahi et al., 2007; Rubal et al., 2007). Chukaew et al. (2008) identified three new acridone alkaloids, cycloatalaphylline-A, N-methylcycloatalaphylline-A, and N-methylbuxifoliadine-E along with two coumarins (auraptene and 7-O-geranylscopoletin) and eight known acridones alkaloids from *A. monophylla.*

Kumar et al. (2010) reported new furoquinoline alkaloids (furoquinoline, 5-hydroxydictamnine) along with β-sitosterol from the heartwood of *A. monophylla*. Sribuhom et al. (2017) isolated 7 new benzoyltyramine alkaloids (atalantums A–G) from the peels of *A. monophylla*. Further, Sombatsri et al. (2018) isolated 3 new limonophyllines (limonophyllines A-C) from the stem of *A. monophylla* along with previously reported limonoids (7-hydroxycycloatalantin and cycloepiatalantin) and 11 acridone alkaloids (N-methylatalaphylline, atalaphylline, citrusinine II, citrusinion I, glycosparvarine, citruscridone, buxifoliadine C, atalaphyllinine, N-methylatalaphyllinine, N-methylcycloatalaphylline A and buxifoliadine E). Posri et al. (2019) isolated a new flavonoid, atalantraflavone along with atalantoflavone, racemoflavone, 5,4'-dihydroxy-(3″,4″-dihydro-3″,4″-dihydroxy)-2″,2″-

dimethylpyrano-(5″,6″:7,8)-flavone, lupalbigenin, anabellamide, citrusinine I, p-hydroxybenzaldehyde, and frideline from the leaves of *A. monophylla*. Four dimeric styrenes – atalantrenes A–D were recorded from the ethanolic extract of *A. monophyla* seeds (Sribuhom et al., 2019).

Sombatsri et al. (2020) documented 4 new benzoyltyramines (atalantums H-K) along with 7 known compounds (atalantums D-G, N-{2-[4-(4-acetoxy-6,7-dihydroxy-3,7-dimethyl-2-octen-1-yl)oxy]phenyl}-ethyl benzamide, N-{2-[4-(4,6,7-trihydroxy-3,7-dimethyl-2-octen-1-yl)oxy]phenyl} ethyl benzamide and N-benzoyltyramine) from the peels of *A. monophylla*. Pailee et al. (2020) identified seven acridone alkaloids (atalantiaphyllines A-G) along with 16 known acridone alkaloids (bosistine, atalaphylline, N-methylatalaphylline, buxifoliadine A, citrusinine II, citrusinine I, glycosparvarine, citbrasine, yukocitrine, cycloatalaphylline-A, N-methylcycloataphylline A, 4-2 (ξ-hydroxy-3-methylbut-3-enyl)-yukocitrine, atalaphyllidine, 5-hydroxynoracronycine, 5-hydroxy-N-methylseverifoline, and N-methylbuxifoliadine E), 3 limonoids (cycloepiatalantin, 7-isovaleroylcycloseverinolide and atalantin), coumarins (hydrangetin, 6,7-dimethoxycoumarin, demethylsuberosin, auraptene, xanthyletin, and 2′,3′-dehydromarmesin) and quinolone derivative (4-methoxy-N-methyl-2-quinolone) from the root and stem dichloromethane extracts of *A. monophylla*. Recently, Nielsen et al. (2021) synthesized atalantrene-B, -C, and -D using styrene dimers from the seeds of *A. monophylla*.

One acridone alkaloid (3,12-dihydro-6,11-dihydroxy-3,3,12-trimethyl-5-(3-methylbut-2-enyl)-pyrano[2,3-c]acridin-7-one), two coumarins (umbelliferone and geranylumbelliferone) were recorded from *A. wightii* (Banerji et al., 1981, 1982). Further, Desai et al. (1977) noted triterpenes (lupeol, lupenone, epi-friedelinol) and stigmasterol from *A. wightii*. Kumar et al. (2009) identified 2 flavones (racemoflavone and atalantoflavone), 4 acridones (atalaphylline, 5-hydroxynoracronycin, citrusinine-I, and citrusinine-II), and triterpene (epi-friedelinol) from leaves of *A. wightii*.

The re-examination of aerial parts of *A. racemosa* identified two new pyranoflavones *viz*. atalantoflavone [8,8-dimethyl-S-hydroxy-2-(4'-hydroxyphenyl)-4H,8H-benzo-(1,2-b:3,4-b')dipyran-4-one] and racemoflavone [8,8-dimethyl-5-hydroxy-2-(4'-hydroxy-3'-methoxyphenyl)-4H,8H-benzo (1,2-b.3,4-6') dlpyran-4-one along with seven coumarin derivatives (xanthyletin, luvangetin, recemosin, xanthotoxin, umbelliferone, rutarin, and rutaretin) and one triterpene (friedelin) (Banerji et al., 1988).

Chang et al. (2018) identified buxifoximes A–C, buxifobenzoate, and 7-O-(7′-peroxygeranyl) coumarin from twigs of *A. buxifolia*. Authors

reported 25 known compounds namely citaldoxime, methyl 4-hydroxybenzoate, methyl 3′-hydroxy-2′-methoxybenzoate, auraptene, 7-[7′-hydroxy-3′,7′-dimethylocta-2′,5′-dienyloxy]-coumarin, 7-(6′-hydroxy-3′,7′-dimethyl-2′E,7′-octadienyloxy)coumarin, peroxyschinilenol, imperatorin, 5-methoxypsoralen, isoimperatorin, 2′,2′-dimethylpyranocoumarin, methyl transferulate, 2-methoxy-6-methylnaphthoquinone, atalaphyllidine, atalaphyllinine, N-methylseverifoline, N-methylatalaphylline, 5-hydroxy-Nmethylseverifoline, glycocitrine-I, severifoline, 5-methoxynoracronycine, N-methylacronicine, 3-taraxeranone, atalantoflavone, and angustifolin. Yang et al. (2012b) identified seven tetranortriterpenoids (6-deacetyl-severinolide, severinolide, acetyl-isoepiatalantin, 7-isovaleroyl cycloepiatalantin, cycloepiatalantin, 7-isovaleroylcycloseverinolide and atalantin) from the root ethanolic extract of *A. buxifolia* and confirmed their structures using 1D and 2D NMR. Yang et al. (2013) isolated two new acridone alkaloids such as 3-methoxy-1,4,5-trihydroxy-10-methylacridone and 2,3-dimethoxy-1,4,5-trihydroxy-10-methylacridone from ethanolic extract of a branch of *A. buxifolia*. Shan et al. (2013) identified a new acridone alkaloid, buxifoliadine along with citrusinine-I, N-methylatalaphylline, severinolid, and cycloseverinolide from the aerial part of *A. buxifolia*. Guo et al. (2015) reported potirucallane-type triterpenoid from the ethanolic extract of roots and its structure was confirmed using 1D, 2D NMR, and HR-ESI-MS. Liang et al. (2020) identified a new alkaloid glycoside (β-D-glu-4,5-dimethoxy-1,6-dihydroxy-10-methyl-acridone) along with 10 known compounds (cycloseverinolide, severinolide, acetylisoepiatalantin, trans-N-p-coumaroy tyramine, β-sitosterol, glycofolinine, citrusinine-I, citrusinine II, 1,4,5-trihydroxy-3-methoxy-10-methyl-acrid one and atalafoline) from the root and rhizome of *A. buxifolia*.

Fraser and Lewis (1973a, b) noted two acronycine analogs (3,12-dihydro-6,11-dihydroxy-3,3,12-trimethylpyrano[2,3-c]acridin-7-one and 5-(3-methylbut-2-enyl) derivative) and two acridone alkaloids (atalanine and ataline) from the bark of *A. ceylanica*. Bowen and Patel (1987) recorded two acridone alkaloids (1,5-dihydroxy-3-methoxy-10-methyl-9(10H)-acridinone and 1-hydroxynoracronycine), pyranoflavone (carpachromene) and benzaldehyde derivative (2,4,5-trimethoxybenzaldehyde) from the leaves of *A. ceylanica*. Further, two new oximes (ataloxime A and B) were identified from seed extract of *A. ceylanica* along with known furanocoumarins (bergapten, xanthotoxin, heraclenin, oxypeucedanin, and imperatorin (Bacher et al., 1999).

Ragasa et al. (2012) reported new triterpenes (retusenol, humulene, friedelin, dischidiol, 5,7-dimethoxy-8-(3-methyl-2-oxybutyl) coumarin and

b-caryophyllene) from the dichloromethane extract of *A. retusa* leaves. Manimaran et al. (2002a) isolated essential oil and identified 10 compounds from fresh leaves. Amongst them, methyl eugenol, sabinene, and elemicin were major compounds. Further, Thirugnanasampandan et al. (2015) analyzed essential oil isolated from leaves of *A. monophylla* during winter (December 2013) and summer (May 2014) from the Western Ghats of southern India. Winter collection revealed 23 compounds with trans-isoeugenol as a major compound. Whereas the summer collection showed 36 compounds with sabinene, trans-asarone, β-pinene, and myrcene observed as major compounds. Essential oil from *A. monophylla* leaves detected 40 compounds. Among them, eugenol (19.76%), sabinene (19.57%), 1,2-dimethoxy-4-(2-methoxyethenyl) benzene (9.84%), beta-asarone (7.02%), and methyl eugenol (5.52%) were detected with higher content (Nattudurai et al., 2017). Similarly, GC-MS analysis of *A. monophylla* essential oil showed the presence of 40 phytochemicals wherein eugenol, sabinene, 1,2-dimethoxy-4-(2-methoxyethenyl) benzene, and β-asarone were noted as major compounds (Baskar et al., 2018). Recently, Jayagoudar et al. (2020) also confirmed the limonene, sabinene, and β-myrcene from the fruit of *A. monophylla*. Das and Swamy (2013) investigated the essential oil composition of *A. monophylla, A. racemosa,* and *A. wightii*. They observed α-asarone, sabinene, eugenol methyl ether, 1,2-dimethoxy-4-(2-methoxyethenyl) benzene, and β-pinene in *A. monophylla*. Similarly, T-cadinol, caryophyllene oxide, β-caryophyllene, spathulenol, β-chellandrene, and decanal noted from *A. racemosa,* and β-caryophyllene, D-limnonene, decanal, β-myrcene, tetra-decanal, caryophyllene oxide and hexa-decylene oxide as the main constituent in *A. wightii*. Das et al. (2015) identified a total of 29 compounds including α-asarone, sabinene, eugenol methyl ether, 1,2-dimethoxy-4-(2-methoxyethenyl) benzene, and β-pinene in *A. monophylla*. In *A. racemosa*, T-cadinol, caryophyllene oxide, β-caryophyllene, spathulenol, β-phellandrene, and decanal were observed in maximum quantities. Similarly, *A. wightii* recorded 64 compounds which include β-caryophyllene, d-limonene, decanal, β-myrcene, tetradecanal, caryophyllene oxide, and hexadecylene oxide. Further, Das and Swamy (2016) noted bioactive compounds from fruit methanolic extracts of *A. monophylla, A. racemosa*, and *A. wightii*. *A. monophylla* and *A. racemosa* possess 27 compounds each, wherein 1,3,4,5-tetrahydroxy-cyclohexane carboxylic acid was the leading candidate in *A. monophylla*, n-hexadecanoic acid in *A. racemosa* and β-sitosterol and stigmasterol in both. Similarly, *A. wightii* revealed 18 compounds including β-sitosterol and stigmasterol were major compounds.

Recently, Saraswathi et al. (2020) identified a total of 27 compounds from the methanolic extract of *A. racemosa* fruit and eight from the methanolic extract of leaves. Major compounds detected in the study were dihydroxyacetone; 4h-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-; 4(1h)-quinolinone, octahydro-1-methyl-; β-asarone; diethyl phthalate; cis-lanceol; β-asarone and catechol. Pang et al. (2020) obtained essential oil from *A. buxifolia* leaves through the hydrodistillation method and examined it by GC-FID and GC-MS. Authors reported 24 compounds including α-pinene, limonene, δ-elemene, α-cubebene, α-copaene, β-bourbonene, β-cubebene, β-elemene, β-caryophyllene, alloaromadedrene, γ-muurolene, γ-himachalene, leden, α-muurolene, calamenene, δ-cadinene, β-germacrene, spatulenol, caryophyllene oxide, glubulol, cubenol, epiglobulol, torreyol, and n-pentadecanal. Among all, β-caryophyllene, caryophyllene oxide, epiglobulol, limonene, α-pinene, and α-copaene were found to be major compounds. Le et al. (2020) analyzed essential oil extracted from the leaves of *A. sessiliflora* and identified 45 compounds by GC-MS. Volatiles reported in the study were linalool, E-β-caryophyllene, ledene, α-humulene, L-α-terpineol, linalyl acetate, (+)-limonene, (+)-spathulenol, geranyl acetate, (–)-globulol and β-myrcene.

Essential oil of *A. roxburghiana* leaves and fruits was analyzed using GC-MS and identified 30 compounds, among them, γ-terpinene, paracymene, β-pinene, and limonene were identified as major compounds (Thai, 2003). Essential oil from branches and leaves of *A. roxburghiana* were investigated through GC and GC/MS and reported 43 compounds which include (E)-2-hexenal, α-thujene, α-pinene, camphene, benzaldehyde, sabinene, β-pinene, myrcene, α-phellandrene, α-terpinene, p-cymene, limonene, (Z)-b-ocimene, (E)-b-ocimene, g-terpinene, terpinolene, linalool, nonanal, terpinen-4-ol, p-cymen-8-ol, methyl salicylate, α-terpineol, citronellol, thymol, carvacrol, β-bourbonene, β-elemene, β-caryophyllene, geranyl acetone, a-humulene, allo-aromadendrene, g-muurolene, t-cadinol, germacrene D, b-oplopenone, β-bisabolene, bicyclogermacrene, g-cadinene, 1,10-di-epi-cubenol, d-cadinene, germacrene B, (E)-nerolidol, (Z)-3-hexenyl benzoate, β-acorenol, spathulenol, caryophyllene oxide, viridiflorol, and α-cadinol (Minh et al., 2010). Hung et al. (2016) isolated essential oil content from leaves, stems, and fruits of *A. guillauminii*. Leaf oil contains 47 compounds which include β-phellandrene, α-phellandrene, and o-cymene. Similarly, a total of 32 compounds were recorded from stem oil in which limonene, sabinene, bicyclogermacrene, bis(2-ethylhexyl) phthalate, and β-caryophyllene were found to be major compounds. Fruit oil was also observed with 34 compounds including sabinene, β-phellandrene, and

α-phellandrene. Further, Pang et al. (2021) examined the chemical composition of fragrant *A. guillauminii* fruit using GC-MS and identified 25 aromatic compounds namely β-pinene, α-phellandrene, d-limonene, β-ocimene, 4-terpineol, phellandral, geranyl acetate, β-elemene, methyleugenol, caryophyllene, α-bergamotene, aromandendrene, elixene, γ-muurolene, acoradien, germacrene d, ledene, δ-cadinene, Selina-3,7(11)-diene, elemicin, globulol, β-spathulenol, viridiflorol, γ-eudesmol, and τ-muurolol (Figures 5.1–5.4).

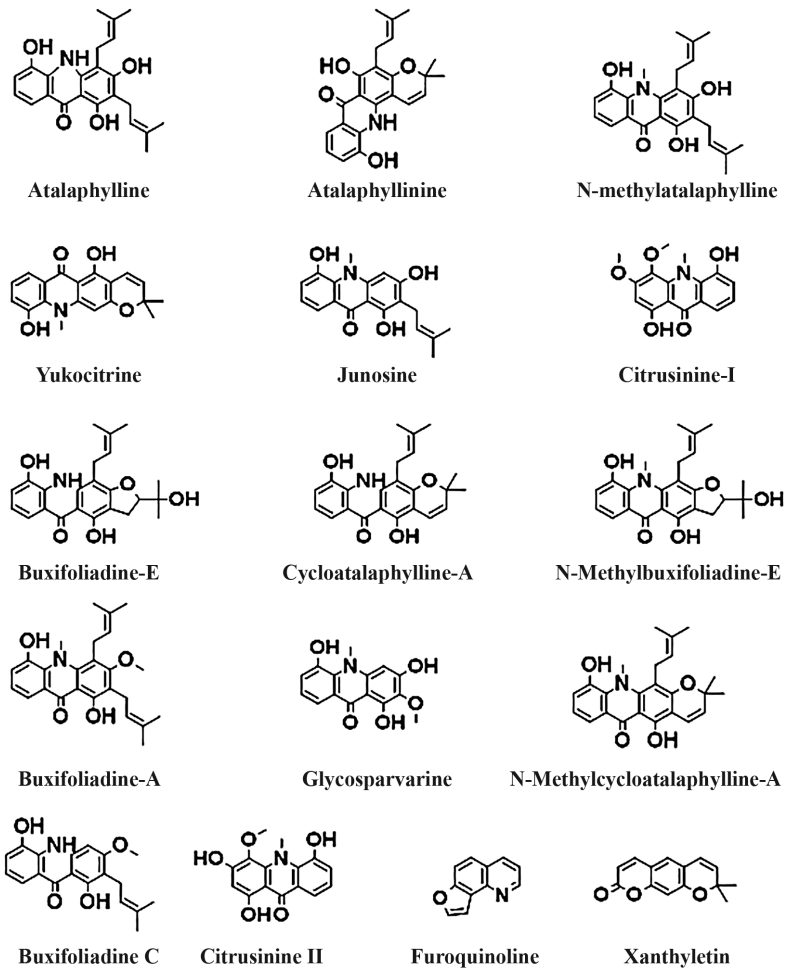


FIGURE 5.1 Alkaloids from genus *Atalantia*.

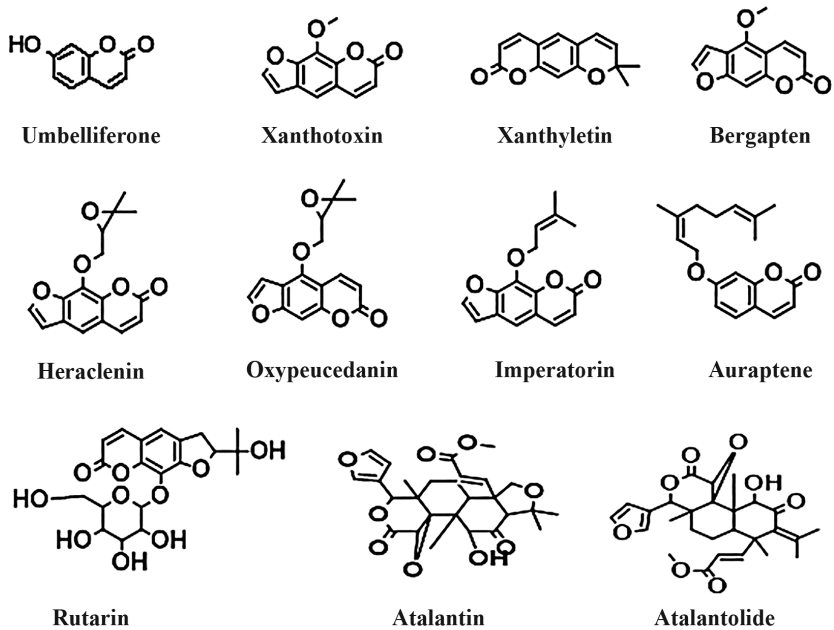


FIGURE 5.2 Coumarins and coumarin derivatives from genus *Atalantia.*

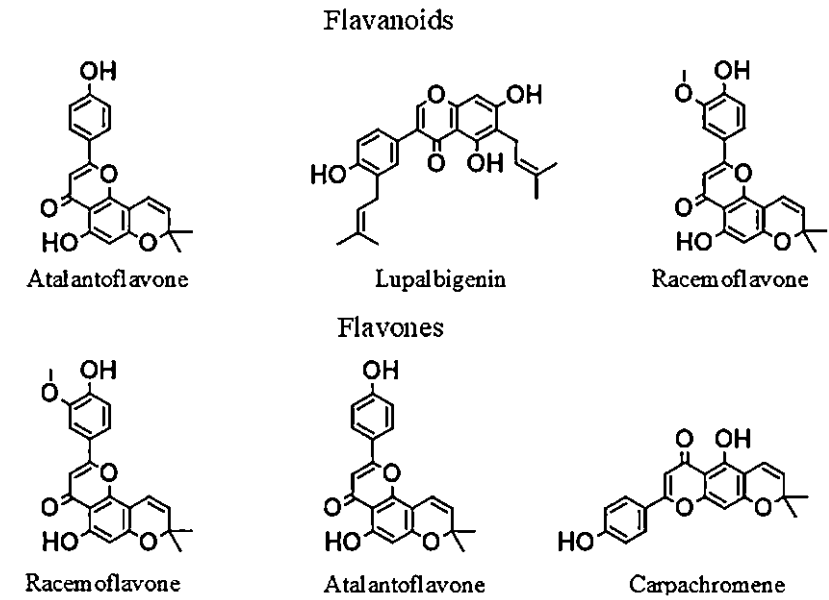


FIGURE 5.3 Flavanoids and flavones from genus *Atalantia.*

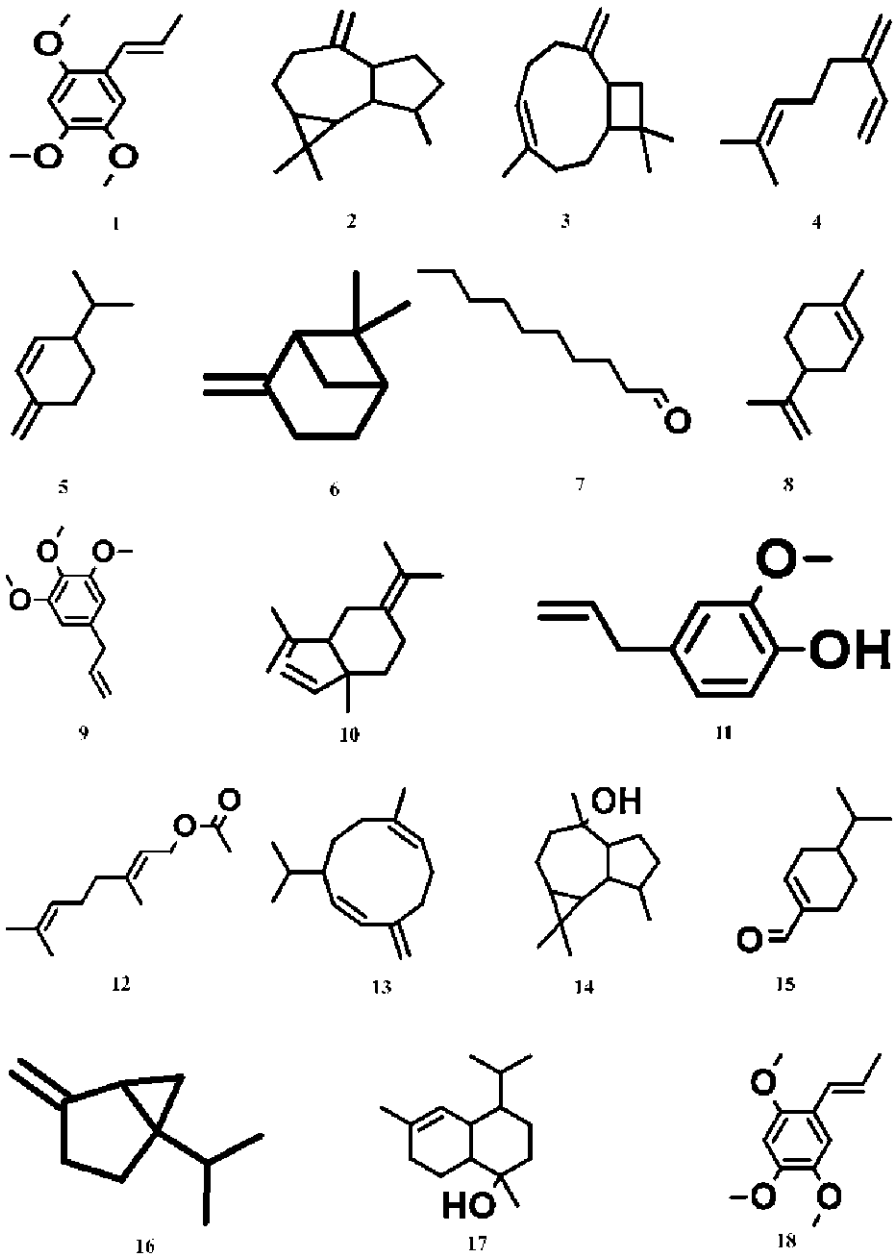


FIGURE 5.4 Volatiles from genus *Atalantia*: (1) alpha-asarone; (2) aromandendrene; (3) beta-caryophyllene; (4) beta-myrcene; (5) beta-phellandrene; (6) beta-pinene; (7) decanal; (8) D-limonene; (9) elemicin; (10) elixene; (11) eugenol; (12) geranyl acetate; (13) germacrene D; (14) globulol; (15) phellandral; (16) sabinene; (17) T-cadinol; and (18) trans-asarone.

5.3 PHARMACOLOGY

5.3.1 ANTI-INFLAMMATORY ACTIVITY

Rao et al. (2008) evaluated methanolic and chloroform root extracts of *A. monophylla* for anti-inflammatory effects in carrageenan-induced albino Wistar rats. Chloroform and methanolic extract (400 mg/kg p.o.) showed a significant reduction in rat paw edema with 48.15 ± 5.90 and 64.67 ± 2.92% inhibition of the maximal paw edema. Raga et al. (2010) orally administered different concentrations of hexane extract of *A. retusa* leaves (0.143, 1.43, and 14.3 mg/kg BW) followed by 0.1 ml of 1% λ-carrageenan single injection at the right foot and 0.9% NSS saline on the left foot of male Sprague-Dawley rats. They observed significantly reduced swelling at a concentration of 1.43 mg/kg BW after 0.5 to 3.0 h of carrageenan injection (1.06 ± 0.19 to 1.20 ± 0.40). Essential oil of *A. sessiliflora* leaves also inhibited macrophage cells from producing NO with an IC_{50} value of 95.94 ± 6.18 µg/mL. Among the different concentrations, 100 µg/mL essential oil significantly inhibited 51.22% NO with 84.67% cell survival (Le et al., 2020).

5.3.2 IMMUNOMODULATORY ACTIVITY

Patil et al. (2015) investigated dried roots of *A. monophylla* for immunomodulatory activity of ethanolic extract fractionated with chloroform, petroleum ether (PE), and methanol. Test animals were orally administrated with different dosages of 10 and 30 mg/kg BW. Among the different fractionated extracts, 30 mg/kg methanolic fraction showed the most significant effect in the *E. coli*-induced abdominal sepsis and carbon clearance test for non-specific immune response. Whereas specific immune response showed the most significant effect on a decrease in footpad edema and an increase in antibody titer. The results indicated that *A. monophylla* has appreciable immunomodulatory potential.

5.3.3 ANTIVIRAL ACTIVITY

Chansakaow et al. (1996) isolated a chlorine derivative – pyropheophorbide (possible antiviral active principle against herpes simplex virus type 2) from leaves chloroform extract of *A. monophylla* and confirmed antiviral activity (EC_{50} 57 µg/mL). Yoshida (1996) grafted *A. monophylla* on citrus with a

severe strain of citrus Tristeza virus (CTV). They observed the infection by double antibody sandwich ELISA with polyclonal antibodies against CTV and conformed appreciable antiviral activities.

5.3.4 ANTIFUNGAL ACTIVITIES

Prasad (1988) reported that essential oil isolated from the leaves of *A. monophylla* exhibited strong inhibitory activities against some pathogenic fungi. Reddy et al. (2010) reported promising antifungal properties from ethanol extract of leaves of *A. monophylla* at 5 mg/mL concentration. The highest MIC values were recorded from *Cryptococcus neoformans* (1 mg/mL) followed by *Candida albicans* (0.95 mg/mL) and *Aspergillus niger* (0.65 mg/mL). Duraipandiyan and Ignacimuthu (2011) examined the antifungal activity of ethyl acetate (EA), hexane, and methanol extracts of *A. monophylla* leaves and noted appreciable antifungal activity from the hexane extract against *Epidermophyton floccosum* (0.125 mg/mL) and *Trichophyton rubrum* 57 (1 mg/mL). EA extract against *Trichophyton mentagrophytes* (0.5 mg/mL), *E. floccosum* (0.125 mg/mL), *Trichophyton simii* (1 mg/mL), and *T. rubrum* 57 (1 mg/mL) was found to be superior. Similarly, methanol extract was active against *T. mentagrophytes* (0.5 mg/mL), *E. floccosum* (0.125 mg/mL), *Trichophyton simii* (1 mg/mL), *Curvularia lunata* (1 mg/mL) and *T. rubrum* 57 (0.125 mg/mL). Aqueous extract and partially purified protein from the leaves of *A. monophylla* were found inhibitory against *Candida albicans* and *Aspergillus fumigatus* (Reddy et al., 2015). They observed higher antifungal activity against *C. albicans* using aqueous (10.37 ± 0.23 mm at 250 μg/mL and 19.28 ± 0.12 mm at 500 μg/mL) and partially purified protein (16.22 ± 0.07 mm at 250 μg/mL and 22.18 ± 0.08 mm at 500 μg/mL) extracts. In contrast, *A. fumigatus* exhibited comparatively poor responses for aqueous and partially purified extracts.

5.3.5 ANTIBACTERIAL ACTIVITY

Thirugnanasampandan et al. (2015) observed strong antibacterial activity from the essential oil of *A. monophylla* against *A. hydrophila* followed by *P. vulgaris, P. aeuroginosa, P. mirabilis,* and *E. coli*. However, the least activity was reported in *K. pneumoniae* and *S. aureus*. The silver nanoparticles obtained from leaves noted excellent antimicrobial activity as compared to standard antibiotics (Mahadevan et al., 2017). The maximum zone of inhibition was

reported in *Staphylococcus aureus* MTCC 737 (37 mm) followed by *Bacillus cereus* MTCC 430 (36 mm) and *Candida albicans* MTCC 227 (34 mm). However, the minimum zone of inhibition (20 mm) was registered with *E. coli* MTCC 1303. They also investigated MIC and minimum bactericidal/fungicidal concentration (MBC/MFC). The lowest MIC and MBC/MFC found in *Bacillus subtilis* MTCC 121, *Staphylococcus aureus* MTCC 737 and *Candida albicans* MTCC 227 (MIC 0.78 μg/mL, MBC/MFC 1.56 μg/mL). Premalatha and Karthi (2017) determined antibacterial activities using a good diffusion method wherein ethanol, chloroform, and EA extracts from leaves of *A. monophylla* were used. Gram-positive (*Staphylococcus aureus*, *Streptococcus epidermidis*, and *Bacillus subtilius*) and gram-negative (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Vibrio cholerae*, *Escherichia coli*, *Proteus vulgaris*, and *Salmonella typhi*) bacteria were used in the study. The ethanolic extract was found to be highly significant from different studied extracts. *Escherichia coli* and *Staphylococcus aureus* showed the highest zone of inhibition. Zinc oxide nanoparticles from *A. monophylla* leaf extract showed the highest antimicrobial potential against *S. aureus* (28 mm zone of inhibition) followed by *C. albicans*, *E. coli*, *B. cereus*, *P. aeruginosa*, *B. subtilis*, *K. pneumoniae*, and *A. niger* (24, 23, 21, 22, 20, 19, and 18-mm zone of inhibition, respectively) (Vijayakumar et al., 2018). Among the different fractionated ethanolic leaf extracts of *A. monophylla*, fractions II and II showed better activity against *Staphylococcus aureus*, *Streptococcus epidermidis*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Vibrio cholerae* and *Proteus vulgaris* (26, 18, 17, 28, 26, 21, 19, 20, and 19 mm zone of inhibition) followed by fraction II (21, 19, 17, 21, 19, 13, 15, 19, and 17 mm zone of inhibition) (Premalatha and Ramar, 2019).

Retusenol, friedelin, and 5,7-dimethoxy-8-(3-methyl-2-oxybutyl) coumarin isolated from the leaves of *A. retusa* showed the highest antimicrobial activity against *Bacillus subtilis* (>55 mm clearing zone and 4.5 activity index each) followed by *Pseudomonas aeruginosa* (17, 16, and 14 mm clearing zone and 0.7, 0.6, and 0.4 activity indices, respectively) and *Staphylococcus aureus* (15, 15, and 16 mm clearing zone and 0.5, 0.5, and 0.6 activity indices, respectively) (Ragasa et al., 2012). Mahadevan et al. (2019) also examined the antimicrobial potential of leaves, fruits, and root bark of *A. monophylla* and *A. racemosa* wherein methanolic leaf extract of both plants showed good antimicrobial potential against *S. aureus* (40 and 38 mm of zone of inhibition, respectively). Potent antimicrobial activity from the leaves essential oil of *A. sessiliflora* was observed against the bacterium,

S. aureus ATCC 43300, *S. aureus* clinical strain, *K. pneumoniae* clinical strain, *E. coli* ATCC 35218, *E. coli* clinical strain with 2, 4, 0.25, 4, and 4% MIC (v/v) and 4, 4, 0.25, 4, and 4% MLC (v/v), respectively. Similarly, four different *Candida* species (*C. albicans* 556 RM, *C. glabrata* clinical, *C. tropicalis* 1011 RM, and *C. parapsilosis* RM) showed 0.5, 2, 1, and 1% MIC (v/v) and 1, 2, 1, and 1% MLC (v/v), respectively (Le et al., 2020).

5.3.6 ANTIOXIDANT ACTIVITY

Ethanol extract from *A. monophylla* leaves revealed promising antioxidant potential (Reddy et al., 2010). They found that 5 mg/mL ethanol extract of *A. monophylla* showed 66, 78, 42.5, 75, and 93% inhibitory activities against DPPH, superoxide, nitric oxide (NO), H_2O_2, and ABTS radicals. Essential oil (250 μg/mL) of *A. monophylla* showed 69.04% inhibition of DPPH free radicals and 66.30% inhibition of linoleic acid peroxidation (Thirugnanasampandan et al., 2015). Aqueous extract and partially purified protein (250 μg/mL) from the leaves of *A. monophylla* revealed 79 and 90% DPPH scavenging activity, 82 and 91% hydrogen peroxide (H_2O_2), 69 and 81% superoxide and 79 and 94% ABTS radical scavenging activities, respectively (Reddy et al., 2015). A number of researchers studied the antioxidant potential of extracts and isolated compounds of different *Atalantia* species (Sujatha et al., 2017; Posri et al., 2019; Pailee et al., 2020).

5.3.7 TOXICITY

Reddy et al. (2015) performed cytotoxicity of aqueous extract and partially purified protein isolated from the leaves of *A. monophylla*. Samples more than 100 μg/mL were found to be the most active against Vero cell lines. Different benzoyltyramines isolated from peels of *A. monophylla* were tested against different cholangiocarcinoma cell lines (KKU-M214, KKU-M213, and KKU-M156) (Sribuhom et al., 2017). Atalantum E showed 4.7-fold higher cytotoxicity against KKU-M156 than the ellipticine standard (IC_{50} 1.97 ± 0.73 μM). Atalantum-A, -E, and -G showed equivalent cytotoxicity against KKU-M214 (IC_{50} 3.06 ± 0.51, 8.44 ± 0.47, and 7.37 ± 1.29 μM, respectively). Atalantum-B and -D also possess stronger cytotoxicity than the ellipticine standard (IC_{50} 2.36 ± 0.20 and 5.63 ± 0.22 μM, respectively). Baskar et al. (2018) performed toxicity on non-target *Danio rerio* (Zebrafish). Around 10 fishes were treated separately with various concentrations of essential oil

(12.5, 25, 50, 75, and 100 mg/L) and found no behavioral changes (reduction in motility) till 96 hours, indicating limited impact on non-target zebrafish (LC_{50} 69.59 ppm).

5.3.8 ANTICANCER ACTIVITY

Among the different compounds isolated from leaves of *A. retusa*, 5,7-dimethoxy-8-(3-methyl-2-oxybutyl) coumarin showed moderate cytotoxicity against human cancer lung adenocarcinoma A549 ($IC_{50,}$ 47.5634 mg/mL), colon carcinoma HCT116 ($IC_{50,}$ 42.4338 mg/mL) and the non-cancer Chinese hamster ovary AA8 ($IC_{50,}$ 46.2751 mg/mL) (Ragasa et al., 2012). Hydrodistilled essential oil from *A. monophylla* leaves showed antigenotoxic and apoptotic activities (Thirugnanasampandan et al., 2016). They tested essential oil on H_2O_2-induced DNA damage in 3T3-L1 cells and observed high DNA-protecting activity at 125 µg/mL extract. The study also revealed dose-dependent inhibition in cancer cell (HeLa) growth (IC_{50} 43.08 ± 0.02 µg/mL). Sombatsri et al. (2018) evaluated the cytotoxicity of 5 limonoids and 11 acridone alkaloids isolated from the stem of *A. monophylla* against KKU-M156 and HepG2 cancer cell lines. Among all studied 16 compounds, buxifoliadine C, N-methylatalaphyllinine, and buxifoliadine E showed cytotoxicity against KKU-M156 and HepG2 cell lines with IC_{50} ranged from 3.39 to 4.1 and 1.43 to 8.4 µg/mL, respectively.

Pailee et al. (2020) recorded 33 compounds from the root and stem dichloromethane extracts of *A. monophylla* and evaluated them for cytotoxicity against human cancer cell lines (MOLT-3, HepG2, A549, and HuCCA-1). Amongst them, three acridone alkaloids namely cycloatalaphylline-A, N-methylbuxifoliadine E, and atalantiaphylline G showed an inhibitory effect against MOLT-3 cell line (IC_{50} 8.0, 5.4, and 9.8 µM, respectively). Acridone alkaloid, 5-hydroxy-N-methylseverifoline showed an inhibitory effect against A549 and HepG2 cell lines (IC_{50} 26.9 and 69.6 µM, respectively). Similarly, atalaphylline, N-methylatalaphylline, and citrusinine I possess inhibitory effects against the HepG2 cell line (IC_{50} values of 82.1, 70.5, and 113.0 µM, respectively). Sombatsri et al. (2020) isolated 11 compounds from peels of *A. monophylla*, and cytotoxicity was assessed against three cancer lines (HeLa, HCT116, and MCF-7) and normal Vero cells line by MTT assay. Higher IC_{50} values (16 to 25 µg/mL) were recorded for the compound atalantum D against all three selected cancer lines. Similarly, atalantum E showed comparatively lower IC_{50} values ranging from 15–18 µg/mL against the studied cancer lines as compared to Vero cells (IC_{50} 80.20 µg/mL).

5.3.9 PESTICIDAL ACTIVITY

Essential oil from *A. monophylla* tested for fumigant action on adults *Callosobruchus maculatus* and *Sitophilus oryzae*. More than 50% mortality in both insects within 12 hours at 160 µL/L concentration was observed. In *C. maculatus* and *S. oryzae*, the highest (70.22 and 65.44%, respectively) mortality was observed at 24 hours at the same concentration. However, 20 µL/L showed 23.78 and 20.44% mortality in *C. maculatus* and *S. oryzae*, respectively (Nattudurai et al., 2017).

5.3.10 ESTERASE ACTIVITY

Nattudurai et al. (2017) studied esterase activity against *C. maculatus* and *S. oryzae* using essential oil isolated from *A. monophylla*. Around 38.29% reduction of esterase activity was observed in *S. oryzae*, at 52.98 µL/L concentration. Similarly, 53.54% esterase inhibitory activity was reported from *C. maculatus*.

5.3.11 GLUTATHIONE (GSH) S-TRANSFERASE ACTIVITY

Increased concentration of essential oil of *A. monophylla* showed decreased glutathione (GSH) S-transferase activity in *S. oryzae* and *C. maculatus* (Nattudurai et al., 2017). In the *C. maculatus*, 43.21% GSH S-transferase activity was observed at 43.28 µL/L concentration.

5.3.12 ANTI-ACETYLCHOLINESTERASE (AChE) ACTIVITY

Nattudurai et al. (2017) studied the impact of *A. monophylla* essential oil on the inhibition of the acetylcholinesterase (AChE) enzyme. In *C. maculatus*, the highest AChE activity (45.21%) was observed at 43.28 µL/L concentration of essential oil. Similarly, maximum AChE activity (44.90%) in *S. oryzae* was observed at 52.98 µL/L concentration. Posri et al. (2019) found that lupalbigenin (isoflavonoid) isolated from leaves of *A. monophylla* showed 79% inhibition which was 1.4-fold stronger than standard tacrine.

5.3.13 MOSQUITOCIDAL/LARVICIDAL ACTIVITY

Luthria et al. (1989) isolated various compounds from n-hexane and methanol extracts of aerial parts of *A. racemosa* and noted antifeedant activity of 7 coumarin derivatives and 17 structurally related coumarins

against *Spodoptera litura* larvae. They observed higher activity in xanthotoxin followed by luvangetin, xanthyletin, and racemosin at 1,000 ppm concentration. Hexane, chloroform, and EA leaf extracts of *A. monophylla* recorded antifeedant, larvicidal, and pupicidal activities on third-instar larvae of *Helicoverpa armigera* (Hubner) (Lepidoptera: Noctuidae). Among them, hexane extract showed significant activities. Out of 12 fractionated extracts, a ninth fraction (1,000 ppm) showed disrupted adult emergence and 100% pupal mortality (Baskar et al., 2009). Muthu et al. (2010) evaluated different *A. monophylla* leaves extracts (hexane, chloroform, and EA) for antifeedant activity, significant activity was recorded in 5% hexane (70.89%) with 14.67% pupation and 16.66% adult emergence. Baskar et al. (2012) studied ovicidal activity from hexane crude extract of *A. monophylla* against *Spodoptera litura* Fab. (Lepidoptera: Noctuidae) wherein maximum activity (61.94%) was observed at 5% concentration. From 12 fractionated extracts, the ninth fraction showed the highest ovicidal activities (75.61% at 1,000 mg/kg). Similarly, 5% hexane, chloroform, and EA leaf extract noted 67.10, 47.49, and 43.36% ovicidal activity against *Helicoverpa armigera* (Lepidoptera: Noctuidae) (Baskar and Ignacimuthu, 2012).

Nattudurai et al. (2017) used *A. monophylla* essential oil for ovicidal activity and adult emergence in *C. maculatus*. The number of eggs laid by females was significantly reduced after 48 h when treated with various concentrations of essential oil. The maximum fecundity (85.56%) was observed in the treated set as compared to the control. Among different concentrations of essential oil, 43.28 µL/L was found to be the most effective against *C. maculatus*. LC_{10} and LC_{20} concentrations showed 62.38 and 55.96% of adult emergence, respectively. *A. monophylla* essential oil tested against larvae of *Aedes aegypti*, *Anopheles stephensi*, and *Culex quinquefasciatus* for larvicidal activity. From all tested mosquitoes, 2nd and 3rd instar larvae showed acute toxicity (Baskar et al., 2018). Among three leaf extracts (methanol, acetone, and water) of *A. monophylla*, acetone extract (1%) showed significant ovicidal activity after 24, 48, and 96 hours (33 ± 2.1, 48 ± 0.0 and 49 ± 0.3%, respectively) (Shiragave, 2018).

Sivagnaname and Kalyanasundaram (2004) studied the mosquitocidal activity of *A. monophylla* leaves methanolic extract against immature mosquito species (*Anopheles stephensi, Culex quinquefasciatus* and *Aedes aegypti*. *C. quinquefasciatus* larvae and *A. stephensi* pupae were found more susceptible (0.14 and 0.05 mg/L, respectively). They also stated that methanolic extracts were found to be safe from predators. Das et al. (2015) investigated the larvicidal activity of essential oil isolated from *A.*

monophylla leaves against *A. aegypti*, *A. stephensi*, and *C. quinquefasciatus*. In all tested species, the highest mortality was noted at 150 ppm essential oil concentration. *A. stephensi* showed 100% mortality (LC_{50} at 50.11 ppm and LC_{90} at 107.69 ppm); whereas in the case of *A. aegypti*, 95% (LC_{50} at 93.2 ppm and LC_{90} at 146.12 ppm) mortality was observed after 24 hrs. Similarly, *C. quinquefasciatus* showed 95% mortality after 48 hours (LC_{50} at 80.8 ppm and LC_{90} at 146.37 ppm). *A. monophylla* essential oil tested against larvae of *Aedes aegypti*, *Anopheles stephensi*, and *Culex quinquefasciatus* for larvicidal activity. The second and fourth instar larvae of all the tested mosquito species showed acute toxicity (100% larvicidal activity) at 50 ppm essential oil. *Aedes aegypti* showed 9.74 and 14.97 ppm LC_{50} and 25.22 and 37.76 ppm LC_{99} in the 2nd and 4th instar larvae, respectively. *Anopheles stephensi* showed 7.91 and 22.58 ppm LC_{50} and 13.34 and 33.72 ppm LC_{99} in the 2nd and 4th instar larvae, respectively. Similarly, *Culex quinquefasciatus* showed 11.73 and 31.42 ppm LC_{50} and 16.44 and 41.13 ppm LC_{99} in 2nd and 4th instar larvae, respectively (Baskar et al., 2018).

5.3.14 REPELLENT ACTIVITY

A. monophylla essential oil was investigated for repellent activity against *A. aegypti*, *A. stephensi* and *C. quinquefasciatus* with 5 volunteers (25–30 days). In *A. aegypti*, 354 min was the maximum protection time found in the 2nd and 3rd volunteers followed by 1st and 5th volunteers (348 min) at 50 ppm. In *A. stephensi*, 366 min was the maximum protection time found in 2nd and 3rd volunteers followed by 1st volunteer (360 min), 4th volunteer (348 min), and 5th volunteer (336 min) at 50 ppm. Volunteer 1st showed the highest protection time (354 min) in *C. quinquefasciatus* at 50 ppm, followed by 2nd (348 min) 3rd and 4th volunteer (342 min), and the least protection time observed in 4th volunteer (336 min) (Baskar et al., 2018). Nattudurai et al. (2017) observed strong repellent activity of *A. monophylla* leaf essential oil against *C. maculatus* and *S. oryzae*. For *C. maculatus* results showed 25.52, 36.22, 52.44, 70.66, and 85.24% repellent activity at 5, 10, 15, 20, and 25 µL, respectively after 3 hours of treatment. Similarly, *S. oryzae* showed 19.75, 28.67, 46.89, 62.67, and 75.24% repellent activity at 5, 10, 15, 20, and 25 µL, respectively.

Pang et al. (2020) examined essential oil and its two compounds (β-caryophyllene and caryophyllene oxide) from *A. buxifolia* leaves for insect-repellent potential. Essential oil exhibited strong repellent activity against *T.*

castaneum and *L. bostrychophila* after 2 and 4 hours. Caryophyllene oxide noted strong repellent activity against *T. castaneum* and *L. bostrychophila* after 2 hours of exposure. However, β-caryophyllene exhibited strong repellent activity after 4-hour exposure. Pang et al. (2021) examined essential oil and its two major constituents (D-limonene and β-pinene) from *A. guillauminii* fruit for repellent activity using the area preference method against *T. castaneum* and *L. serricorne*. About 78.63 and 15.73 nL/cm^2 concentration of essential oil. D-limonene and β-pinene showed approximate repellent activity compared with the positive control (DEET) against *T. castaneum* adults after 2 and 4 h of exposure. Whereas only D-limonene showed the strongest repellent activity at 78.63 nL/cm^2 concentration against *L. serricorne* adults after 2 h of treatment. The findings from the essential oil of different *Atalantia* species could be used for the development of mosquito repellents.

5.3.15 ANTI-ALLERGIC ACTIVITY

Chukaew et al. (2008) performed anti-allergic activity from *A. monophylla* and its compounds such as buxifoliadine-E, citrusinine-I, and N-methylcycloatalaphylline-A found effective against antigen-induced b-hexosaminidase. N-methylatalaphylline, atalaphylline, N-methylataphyllinine, auraptene, and 7-O-geranylscopoletin failed to exhibit the activity. They also observed that these compounds possessed stronger anti-allergic activity than the clinically used drug – ketotifen fumarate. They also suggested that buxifoliadine-E could provide a platform for the structure-based design of acridone-class antiallergic agents.

5.3.16 ANTI-DIABETIC ACTIVITY

Mahesh et al. (2012) orally administrated methanolic extract of *A. monophylla* bark (50–200 mg/kg, p.o) to the alloxan-induced (200 mg/kg, i.p.) Swiss albino mice for 14 days and serum glucose and lipid content (total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, and very low-density lipoprotein) were analyzed. Significant reduction in serum glucose level was observed at 100 and 200 mg/kg, p.o extract concentration (151.3 ± 9.57 and 124.9 ± 7.27 mg/dL, respectively). At the same concentration, total cholesterol, triglyceride, low-density lipoprotein, and very low-density lipoprotein showed significant reduction (128.4 ± 2.48, 127.82 ± 5.82, 58.1 ± 3.1, and 25.56 ± 1.26 mg/dL for 100 mg/kg and 110.5 ± 4.03, 110.62 ± 4.32, 32.46 ± 4.8, and 22.12 ± 1.16 for 200 mg/

kg, respectively) and high-density lipoprotein showed significant increment (47.89 ± 1.4 and 54.27 ± 2.9 mg/dL, respectively). Oral glucose tolerance levels in male Wistar rats treated with 100 and 200 mg/kg p.o showed a significant increase in glucose tolerance after 90 min. The findings proved the antidiabetic potential of *A. monophylla.*

5.3.17 WOUND HEALING ACTIVITY

Manimaran et al. (2002b) noted that 2 and 5% cream with leaf volatile oil of *A. monophylla* showed better-wound healing activity through the excision wounding method in rats than the standard drug nitrofurazone.

5.3.18 HEPATOPROTECTIVE ACTIVITY

Fernando and Soysa (2014) induced hepatotoxicity on porcine liver slices treated with an aqueous extract of *A. ceylanica* for 2 hours. Plant extract (2 mg/mL) showed a significant reduction of leakage of porcine liver slices in alanine transaminase (ALT), aspartate transaminase, and lactate dehydrogenase medium. The same concentration of plant extract with 5 M ethanol significantly reduced the formation of lipid peroxides.

5.3.19 ANTINOCICEPTIVE ACTIVITY

Raga et al. (2010) orally administrated hexane extract of *A. retusa* leaves followed by a single dose of 1% formalin injection to Sprague-Dawley male rats. Hexane extract (1.43 mg/kg BW) showed significant analgesic potential (14.33 ± 3.14 paw licking and 34.85 ± 14.28% inhibition) as compared to paracetamol (15.67 ± 4.41 paw licking and 28.80 ± 20.05% inhibition). Similarly, ICR male mice orally administered with *A. retusa* extract with 1% glacial acetic acid single injection revealed significant analgesic effect at 1.43 and 14.3 mg/kg BW (2.89 ± 3.06 and 6.78 ± 6.30 writhes and 90.51 ± 10.05 and 77.73 ± 20.70% inhibition, respectively) when compared with paracetamol (19.78 ± 10.20 writhes and 35.03 ± 33.50% inhibition).

5.3.20 INSECTICIDAL ACTIVITY

Pang et al. (2020) examined essential oil and its two compounds (β-caryophyllene and caryophyllene oxide) from *A. buxifolia* leaves against *Tribolium castaneum, Lasioderma serricorne,* and *Liposcelis*

bostrychophila. The essential oil showed significant contact toxicity against all three insects with LD_{50} values of 23.9 µg/adult, 15.2 µg/adult, and 54.6 µg/cm^2, respectively. The stronger contact toxicity against *L. serricorne* and *L. bostrychophila* was noted from caryophyllene oxide (LD_{50} 45.7 µg/adult and 46.4 µg/cm^2, respectively). β-caryophyllene also showed significant contact toxicity against *T. castaneum* (LD_{50} 36.0 µg/adult). Recently, Pang et al. (2021) examined essential oil and its two major constituents (D-limonene and β-pinene) from *A. guillauminii* fruit for an insecticidal property using fumigant and contact toxicity assay against *T. castaneum* and *L. serricorne*. They observed an increased mortality rate with increasing concentration. Significant fumigant toxicity has been reported when total essential oil was used. D-Limonene and β-pinene registered with LC_{50} values of 6.4, 6.3, and 14.5 mg/L for *T. castaneum* and 48.4, 13.7, and 28.3 mg/L for *L. serricorne*, respectively. Similarly, in the contact toxicity assay, D-limonene, and β-pinene noted LD_{50} values of 15.8, 14.2, and 21.6 µg/adult for *T. castaneum* and 12.2, 13.1, and 61.5 µg/adult *L. serricorne*, respectively.

5.3.21 AROMATASE INHIBITION ACTIVITY

Pailee et al. (2020) recorded a total of 33 compounds from the root and stem dichloromethane extracts of *A. monophylla* and further used to test aromatase inhibition activity. A total of 16 acridone alkaloids showed promising aromatase inhibitory activity with IC_{50} values ranging from 0.08 to 2.0 µM. Atalantiaphylline D was found to be more potent with IC_{50} value of 0.08 µM as compared to positive control ketoconazole (IC_{50} 2.4 µM).

KEYWORDS

- **anti-acetylcholinesterase**
- ***Atalantia***
- ***Atalantia monophylla***
- **citrus tristeza virus**
- **corymbose cyme**
- **minimum bactericidal concentration**

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CHAPTER 6

Traditional Drug *Aloe vera* (L.) Burm. f. – Phytochemistry and Biological Properties

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6.1 INTRODUCTION

Aloe vera (L.) Burm. f. is cultivated in warm temperate to tropical regions around the world. It's a clump-forming succulent cactus. The main rosette grows up to about 60 cm high and produces little offset rosettes continually. In winter and spring, *Aloe* bears small tubular flowers. It has synonyms such as *Aloe barbadensis* Mill., *Aloe chinensis* Loudon, *Aloe indica* Royle, *Aloe variegata* Forssk, and *Aloe vulgaris* Lam.

Aloe is a genus of therapeutic plants with a distinguished history of therapeutic use. *Aloe* shows free radical scavenging activity, and anti-proliferative, and immune stimulatory properties (Harlev et al., 2012). *A. vera* has been used for over 5,000 years. Throughout history, it has been an enchanted plant, virtually a panacea accomplished in curing numerous ailments in human beings. In the last 20 years, after a sequence of proven research, those authors highlight the characteristics of this plant, whose confidence has been concealed behind a blanket of botanical and pharmacological puzzles that begin to yield some responses (Malik and Zarnigar, 2003). *A. vera* is popular for its important medicinal properties and is one of the richest natural sources with numerous benefits for human beings. *Aloe* shows more than 200 various biologically active constituents. Several biological properties associated with *Aloe* species are donated by the innermost gel of the leaves. Most of

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the investigation has been focused on the biological activities of the many species of *Aloe*, which contain anti-bacterial and anti-microbial activities of the non-volatile ingredients of the leaf gel. *Aloe* species are extensively dispersed in the African and eastern European regions and are spread nearly all over the world. In addition, *A. vera* has also been endorsed for constipation, gastrointestinal disorders and the immune system lacks. *Aloe* gel and its several phytocomponents are having numerous biological properties that help to recover health and avoid disease situations (Radha and Laxmipriya, 2015).

In addition to their numerous uses in traditional therapeutics, the *Aloes* have also been used as constituents of cosmetic formulations and in the food and beverage industries. *Aloe* can be used in pills, sprays, ointments, lotions, liquids, drinks, jellies, and creams and for relief from constipation and treating pimples (Deokule and Mokat, 2004). Many of the health benefits associated with *Aloe vera* have been attributed to the polysaccharides contained in the gel of the leaves (Josias, 2008). *A. vera* has been traditionally used to treat skin injuries such as burns, cuts, insect bites, eczemas, etc. It also proves to be beneficial in treating digestive disorders due to its anti-inflammatory, antimicrobial and wound-healing properties. Investigation into this medicinal plant has been expected at authenticating traditional uses and spreading of the mechanism of action as well as identify the compounds responsible for these activities. Similarly, new actions have been inspected for *A. vera* and its active phyto-constituents. New pharmacological data investigation has specifically revealed that most studies mention anti-cancer action, skin, and digestive protective activity as well as anti-microbial properties. Medical trials have been conducted just by *Aloe vera*, but not through isolated compounds; so it would be stimulating to study the medical effect of related metabolites in dissimilar human situations and pathologies. The promising outcomes of these studies in basic investigation inspire a better number of medical trials to test the medical application of *A. vera* and its main compounds, mostly on bone protection, cancer, and diabetes (Sánchez et al., 2020).

6.2 PHYTOCHEMISTRY

More than 200 compounds were found in *Aloe vera*, about 110 compounds were isolated in plant such as Aloesin; neoaloesin A; 8-C-glucosyl-(R)-aloesol; 8-C-glucosyl-7-methoxy-(R)-aloesol; 8-C-glucosyl-(S)-aloesol; 8-C-glucosyl-7-methoxy-(S)-aloesol; 8-C-glucosyl; 7-O-methylaloediol; 8-glucosyl-(2'-O-cinnamoyl)-7-O-methylaloediol A; 8-glucosyl-(2'-O-

cinnamoyl)-7-O-methylaloediol B; C-20-decoumaroyl-aloeresin G; aloeresin E; isoaloeresin D; iso-rabaichromone 8-[C-β-D-[2-O-(E)-cinnamoyl]; glucopyranosyl]-2-[(R)-2-hydroxypropyl]-7-methoxy-5-methylchromone; aloeresin D; rabaichromone; allo-aloeresin D; aloeresin K; aloeresin J; 8-C-glucosyl-noreugenin; 4'-O-glucosyl-isoaloeresin DI; 4'-O-glucosyl-isoaloeresin DII; aloeresin A; 7-O-methyl-aloeresin A; 9-dihydroxyl-2'-O-(Z)-cinnamoyl-7-methoxy-aloesin; 60-O-coumaroyl-aloesin; 7-methoxy-60-O-coumaroyl-aloesin; aloeveraside B; aloeveraside A; aloin A; aloin B; 60-O-acetyl-aloin A; 60-O-acetyl-aloin B; 10-hydroxyaloins A; 10-hydroxyaloins B; aloinoside A; aloinoside B; 7-hydroxyaloin A; 7-hydroxyaloin B; 7-hydroxy-8-O-methylaloin A; 7-hydroxy-8-O-methylaloin B; 60-malonylnataloin A; 60; malonylnataloin B; homonataloside B; elgonica dimer A; elgonica dimer B; aloindimer A; aloindimer B; aloindimer C; aloindimer D; aloe-emodin-11-O-rhamnoside; chrysophanol; emodin; physcione; aloe-emodin; nataloeemodin; aloesaponarin I; aloesaponarin II; madagascine; 3-Geranyloxyemodin; Rhein; apigenin; luteolin; isovitexin; isoorientin; saponarin; lutonarin; kaempferol; quercetin; myricetin; quercitrin; rutin; catechin; epicatechin; cinnamic acid; p-coumaric; caffeic acid; ferulic acid; sinapic acid; 5-p-coumaroylquinic; chlorogenic; 5-feruloylquinic; caffeoylshikimic; 5-p-cis-coumaroylquinic; 3-(4-hydroxyphenyl) propanoic acid; methyl 3-(4-hydroxyphenyl) propionate; 7-demethylsiderin; feralolide; dihydrocoumarin; dihydrocoumarin ethyl ester; aloenin A; aloenin B; p-coumaroyl aloenin; aloveroside A; feroxidin; 1-(2,4-dihydroxy-6-methylphenyl) ethanone; p-anisaldehyde; salicylaldehyde; p-cresol; pyrocatechol; gentisic acid; gallic acid; vanillic acid; syringic acid; ascorbic acid; cycloartanol; 24-methylene-cycloartanol; lophenol; 24-methyl-lophenol; 24-ethyl-lophenol, etc. (Kahramanoglu et al., 2019).

The aqueous extract of *A. vera* showed the presence of proteins, carbohydrates, phenols, tannins, steroids, terpenoids, and glycosides (Bista et al., 2020).

The most examined active phytoconstituents are aloe-emodin, aloesin, aloin, and emodin as well as acemannan (Sánchez et al., 2020). *A. vera* leaves contain a diverse array of compounds including anthraquinones (e.g., aloe-emodin), anthrones, and their glycosides (e.g., 10-(1,5'anhydroglucosyl)-aloe emodin-9-anthrone, also known as aloin A and B), chromones, carbohydrates, proteins, glycoproteins, amino acids, organic acids, lipids, sugars, vitamins, and minerals (Figure 6.1) (Roy, 2012; Saeed et al., 2004; Patidar et al., 2012).

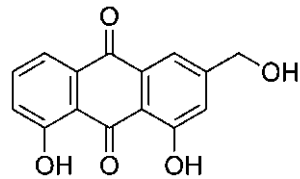


FIGURE 6.1 Aloe emodin.

A study of different agroclimatic zones and their effect on the total phenolic content and antioxidant potential of this plant showed significant differences. Alkaloids, phenols, flavonoids, saponins, and terpenes were the main phytochemicals present in all accessions. Extracts of highland and semi-arid zones possessed maximum antioxidant potential. Accessions from tropical zones showed the least antioxidant activity in all assays (Kumar et al., 2017).

HPTLC analysis showed the presence of 2.74% and 0.543% w/w of berberine and gallic acid, which can be used for its standardization (Patel et al., 2012). Hydroxycinnamics, anthrones, and chromones are the most represented phenolics. The 5-methylchromones aloesin, aloeresin A, and aloesone were the most active among the pure secondary metabolites tested. The results suggest that several compounds are likely to contribute to the overall radical scavenging activity (Lucini et al., 2015). The polysaccharide isolated by alcohol precipitation of *A. vera* mucilaginous gel to have a Man:Glc:Gal:GalA:Fuc:Ara:Xyl ratio of 120:9:6:3:2:2:1 by traces of Rha and GlcA. Linkage investigation of the endo-(1→4)-beta-d-mannanase-treated sample yielded Manp-(1→(about 26%), 4-Manp (about 53%), 2,4-Manp (about 3%), 3,4-Manp (about 1%), 4,6-Manp (about 1%), 4-Glcp (about 5%), 4-Xylp (about 1%), Xylp-(1→(about 2%), Galp-(1→(about 5%), and traces of 4,6-Galp and 3,6-Galp. Hydrolysis with robust acids produced a mixture of short oligosaccharides and an acid-resistant fraction containing greater comparative fractions of Manp-(1→, Araf-(1→, Xylp-(1→, and 4-Xylp than the majority polysaccharide. NMR investigation of oligosaccharides generated through endo-(1→4)-beta-D-mannanase and acid hydrolysis revealed the presence of di-, tri-, and tetrasaccharides of 4-beta-Manp, beta-Glcp-(1→4)-Man, beta-Glcp-(1→4)-beta-Manp-(1→4)-Man, and beta-Manp-(1→4)-[alpha-Galp-(1→6)]-Man, reliable by a support containing alternating →4)-beta-Manp-(1→ and →4)-beta-Glcp-(1→ residues in an approximately 15:1 ratio. Analysis of the sample treated sequentially with endo-(1→4)-beta-d-mannanase and

alpha-D-galactosidase indicated that the mainstream of alpha-Galp-(1→ residues were linked to O-2, O-3, or O-6 of →4)-beta-Manp-(1→ residues, with approximately 16 →4)-beta-Manp-(1→ residues between side chains. Statistics provide a direct indication of a previously proposed glucomannan backbone but draw into query before proposed side-chain structures (Chow et al., 2005). Fractions of leaf gel from *A. barbadensis* were ready by gel infusion by using DEAE Sephadex A-25 and Sepharose 6B as well as Sephadex G-50 columns. These were tested by *in-vitro* evaluations for the proliferation of human usual dermal and baby hamster kidney cells. The glycoprotein fraction encouraged cell growth, although the neutral polysaccharide fraction didn't display any growth inspiration. Furthermore, the polar-colored glycoprotein fraction powerfully reserved the *in-vitro* assessments. An active glycoprotein fraction (protein 82% and carbohydrate 11%) inspected on polyacrylamide gel electrophoresis (PAGE) and SDS-PAGE displayed a single band. Its molecular weight was 29 kD on a Sephadex G-50 column and its iso-electric point was pH 6.8. Immuno-blotting after SDS-PAGE displayed that the glycoprotein was calm of two subunits (14 kD). Deglycosylation of glycoprotein (Pg21-2b fraction) through trifluoromethanesulfonic acid provides a protein band with a molecular weight of 13 kD on SDS-PAGE. The colored glycoprotein fraction was revealed on SDS-PAGE to be a mixture with a molecular weight of 18 kD–15 kD. It was later hydrolyzed by 10% H_2SO_4 to produce phenolic substances (Yagi et al., 1997).

Gel fresh weight of *Aloe vera* increased as a result of a combination of mycorrhizal fungi and phosphate-solubilizing bacteria. Aloin content showed a higher amount under 25% of the water requirement and biofertilizers inoculation (Khajeeyan et al., 2021).

The LC-QTOF-MS results of *Aloe vera* leaves extract in the optimized condition of MAE indicated a total of 32 phenolics and 29 saponin compounds, including phenols, triterpenoids, and steroid saponins. The FTIR (Fourier transform infrared spectroscopy) results also confirmed the existence of these biological compounds in the extract of leaves (Akbari et al., 2021). The reversed-phase high-performance liquid chromatographic (RP-HPLC) method for the development and validation of simultaneous quantitative estimation of berberine and aloe-emodin in polyherbal formulation, revealed that this novel isocratic HPLC method is well validated, reliable, and can be used for routine analysis of berberine and aloe-emodin in polyherbal formulations (Jain et al., 2021).

6.3 PHARMACOLOGY

Gastrointestinal activities, hepato-protective properties, and beneficial effects against skin problems *viz*., wounds, injuries, and infective diseases are amongst the most regularly mentioned properties of *Aloe* spp. Numerous activities of *Aloe* spp. defined in traditional drugs have been the topic of current in-vitro and in-vivo studies as well as clinical trials. Owed to the positive conclusions, dissimilar preparations of *Aloe* spp. are nowadays present in medicinal markets such as *Aloe* cosmetic products. On the other hand, there are numerous traditional healing properties of *Aloe* spp. which have not been studied and necessitate assenting investigational or medical surveys. It is expected that the current study could arouse more studies on the unexplored features of the therapeutic properties of *Aloe* spp. (Akaberi et al., 2016). Many of the health benefits associated with *A. vera* have been attributed to the polysaccharides contained in the gel of the leaves. These biological activities include the promotion of wound healing, hypoglycemic or anti-diabetic effects, anti-fungal activity, anti-inflammatory, anti-cancer, gastroprotective, and immunomodulatory properties. While the known biological activities of *A. vera* will be briefly discussed, more highpoint lately revealed the effects and applications of the leaf gel. These effects contain the potential of entire leaf or internal filet gel liquid preparations of *A. vera* to improve the intestinal absorption and bioavailability of co-administered combinations and improvement of skin permeation. Additionally, significant pharmacological requests such as the use of dried *A. vera* gel powder as an excipient in continued-release medicinal dosage forms will be delineated (Hamman, 2008). A number of useful effects of *A. vera* have been stated, counting with immunomodulatory, hypoglycemic, wound, and burn healing, anti-cancer, anti-fungal, anti-inflammatory, and gastro-protective properties. These useful therapeutic properties of *A. vera* have been working for a number of profitable applications. It is predictable that further information will be available at a faster rate in the near future, subsequent to improved applications (Maan et al., 2018). *A. vera* has various medicinal properties such as antitumor, anti-arthritic, anti-rheumatoid, anti-cancer, and anti-diabetic properties (Radha and Laxmipriya, 2015). Fresh leaves showed total antioxidant capacity, DPPH radical scavenging assay, and reducing the power of fresh leaves was found to be 103.49 ± 0.24%, 81.91 ± 0.04%, and 67.08 ± 0.85% of dry mass, respectively. *A. vera* can be used as a medicinal herb but its toxicological properties are yet to be studied (Bista et al., 2020). The antioxidant property of the optimized extract was also evaluated based

on IC_{50} values of DPPH and ABTS assays and the compared results with Ascorbic acid, *Aloe* extract indicated good antioxidant activity (Akbari et al., 2021).

6.3.1 ANTI-FUNGAL ACTIVITY

The research work carried out showed an antifungal effect of combined antifungal creams (AFCs) with turmeric essential oil (TEO) or *Aloe vera* gel (AVG) (Ogidi et al., 2021). The gel preparation activity as a rejuvenation agent at a concentration of 6% (Kartika et al., 2021).

6.3.2 ANTI-CANCER ACTIVITY

A new drug delivery mechanism was developed by Murugesan et al. (2021) with *A. vera* extract in phospholipids to develop robust and effective anti-carcinogenic gel material. The anti-cancer significance of Aloe-emodin, an anthraquinone complex present in *A. arborescens* leaves, on human glioblastoma cell line U87MG was tested. U87MG were treated with several concentrations of Aloe-emodin, i.e., 20 and 40 μM at different times, such as 24, 48, and 72 hr. Cell growth was checked by everyday cell count afterward treatments. Growth investigation presented that Aloe-Emodin significantly decreased the explosion of U87MG in a time and dose-reliant manner. FACS study proves a block of the cell cycle in the S and G2/M phases. Aloe-Emodin can be influenced as well apoptosis with discharging of apoptosis-inducing factors: PARP and Lamin leading to nuclear reduction. Furthermore, the revelation of U87MG to Aloe-emodin condensed pAKT phosphorylation. Aloe-emodin inhibition of U87MG growth is a consequence of more mechanisms together. Now authors informed that Aloe-emodin has a specific growing inhibition on U87MG also in in-vivo. The evolution of U87MG, hypodermically injected in exposed mice with severe combined immunodeficiency, is inhibited lacking any considerable toxic effects on the animals after Aloe-emodin treatment. Aloe-emodin strength signifies an abstractly novel lead antitumor adjuvant drug (Arcella et al., 2018). The anti-genotoxic and chemo-preventive effect of *Aloe barbadensis* (polysaccharide fraction) on benzo[a]pyrene (B[a]P)-DNA adducts were inspected *in-vitro* and *in-vivo*. The results recommend that the inhibitory effect of *Aloe* on BPDE-I-DNA adduct formation might have a chemo-preventive effect by inhibition of B[a]P preoccupation (Kim and Lee, 1997).

6.3.3 ANTI-DIABETIC POTENTIAL

Oral administration of *A. vera* gel extract caused a significant decrease in cholesterol and triacylglycerols by 31% and 20.61%, respectively as compared to the untreated diabetic group (Mohamed, 2011). Atiba et al. (2019) reported that *A. vera* could be useful as a therapy for diabetic keratopathy.

6.3.4 WOUND HEALING PROPERTY

The combination of *A. vera* and ASCs formed a novel hydrogel scaffold in which the incorporation of *A. vera* with ASCs significantly enhanced the expression level of cytokines and growth factors and finally resulted in improved wound repair and regeneration (Oryan et al., 2019). In one investigation it was found that *A. vera* gel enhanced wound healing through the increased blood supply, which augmented oxygenation as an outcome (Davis et al., 1989).

The influence of *A. vera* on the glycosaminoglycan components of the matrix in a healing wound was studied. Wound healing is a dynamic and complex arrangement of events of which the main one is the synthesis of extracellular matrix components. The initial phase of wound healing is characterized by the placing down of a temporary matrix, which is then followed by the creation of granulation tissue and the synthesis of elastin and collagen. The temporary matrix or the ground substance includes proteoglycans and glycosaminoglycans, which are protein glycosaminoglycan conjugates. The influence of *A. vera* on the content of glycosaminoglycan and its kinds in the granulation tissue of healing wounds is noteworthy. The authors also informed the levels of insufficient enzymes elaborate in matrix metabolism. The quantity of ground substance produced was found to be higher in the treated wounds and specifically, dermatan sulfate and hyaluronic acid levels were improved. The levels of the informed glycohydrolases increased on treatment with *A. vera*, indicating improved turn-over of the matrix. Both topical and oral treatments with *A. vera* were found to have a positive influence on the synthesis of glycosaminoglycans and thereby usefully moderate wound healing (Chithra et al., 1998).

6.3.5 OBESITY

Misawa et al. (2012a) reported that *A. vera* gel is useful in reducing diet-induced obesity. Administration of dried *A. vera* gel powder to diet-induced

obesity rats did not display any significant effect on reduction in the body weight and food intake (Misawa et al., 2012b).

6.3.6 ORAL CAVITY DISEASE

Meshram et al. (2018) reported that *A. vera* is useful in treating oral cavity disease. Babaee et al., (2012). conducted a double-blind clinical trial to evaluate the topically administered A. vera gel on oral cavity minor aphthous. It was concluded that *A. vera* 2% oral gel is not only effective in decreasing the patient's pain score and wound size, but also decreased the aphthous wound healing period.

6.3.7 ANTI-MICROBIAL ACTIVITY

Auta et al. (2017) investigated the anti-microbial activity of *A. vera* crude methanolic extract. The extract had zones of inhibition with *S. aureus* 25.0 mm, *P. aeruginosa* 22.0 mm, *E. coli,* 5.0 mm, and *S. typhi* 4.0 mm, respectively.

A. vera (*A. barbadensis*) has been recommended for a wide variety of ailments but its use in dentistry is restricted. The uses of the plant describe an in-vitro examination that compared the anti-microbial efficiency of *A. vera* tooth gel with two popular, commercially obtainable dentifrices. The initial results displayed that *A. vera* tooth gel and the toothpaste were equally effective against *Streptococcus mutans, Prevotella intermedia, Lactobacillus acidophilus, Candida albicans, Enterococcus faecalis,* and *Peptostreptococcus anaerobius*. *A. vera* tooth gel improved anti-bacterial effect against *S. mitis* (George et al., 2009). Habeeb et al. (2007) investigated the anti-microbial properties of the innermost leaf gel constituent of *A. barbadensis* and has used a number of different, simple *in-vitro* evaluates to find a systematic basis for the potential use by *A. vera* on a range of clinically applicable bacteria. The bacteria used included *Shigella flexneri,* methicillin-resistant *Staphylococcus aureus*, *Enterococcus bovis,* and *Enterobacter cloacae*. This revealed that *A. vera* has an anti-microbial effect, though, the microtiter assay allows high throughput showing, under similar circumstances, and is less wasteful of plant material (Habeeb et al., 2007).

Anti-bacterial activity of leaf and gel extracts of *A. vera* were tested against skin infections isolates. Around 115 bacterial strains were isolated from skin wounds, burns, and acne of several patients, and the strains were identified through conventional approaches. Of the total isolates, 90% of the

organisms were gram-positive and 10% were gram-negative. The gel extracts of *A. vera* displayed anti-bacterial activity while the leaf extracts displayed no such activity. This data presented promising outcomes in the case of *A. vera* related to five broad-spectrum antibiotics. Moreover, the study also established that the skin infectious isolates were resilient in contradiction to broad-spectrum antibiotics (Bashir et al., 2011).

6.3.8 ANTI-INFLAMMATORY ACTIVITY

Davis et al. (1989) have assessed the spectrum of anti-inflammatory activity of *A. vera*. Croton oil was used in an experimental model of inflammation to achieve the oral activity and time-dependent treatment of *A. vera*. *A. vera* was active in all models of inflammation. *A. vera* was particularly active in contradiction of gelatin-induced and kaolin-induced edema and contrast, had minimal activity when tested against dextran-induced edema. The oral activity of *A. vera* was established to be dependent on the occurrence of anthraquinones. The many irritant-induced edema models provide a broad spectrum of anti-inflammatory activity for *A. vera* (Davis et al., 1989). A new anti-inflammatory agent has been isolated from *A. barbadensis*. At a dose of 200 microg/mouse ear, showed topical anti-inflammatory activity corresponding to 200 µg/mouse ear of hydrocortisone. There was no decrease in thymus weight produced by treatment with one for any of the doses tested, although 200 µg/mouse ear of hydrocortisone caused a 50% reduction in thymus weight (Hutter et al., 1996).

6.3.9 ANTI-WRINKLE ACTIVITY

Aloe stimulates fibroblast which produces elastin fibers and collagen making the skin extra flexible and less wrinkly (Davis, 1993).

6.3.10 IMMUNOMODULATORY ACTIVITY

Polysaccharides isolated from the gel of *Aloe* species have been known to have varied biological activities, with immunomodulatory and antitumor activities. The molecular size-immunomodulatory activity relationship of modified *Aloe* polysaccharide (MAP) was studied. Crude MAP (G2E1) was prepared from the gel of *A. vera* that was partly absorbed with cellulase. Proteins in crude MAP were detached by passage through a DEAE-Sephacel column and formerly the protein-free MAP (G2E1D) was additionally

detached into three fractions. Immunomodulatory activities of MAP preparations were inspected on a mouse macrophage cell line, RAW 264.7 cells, and in the ICR strain of a mouse implanted with sarcoma 180 cells. Authors found that polysaccharides between 400 and 5 KDa show the greatest strong macrophage-activating activity as determined by augmented cytokine production, expression of surface molecules, nitric oxide (NO) release, and phagocytic activity. In agreement with the *in-vitro* activity, polysaccharides between 400 and 5 KDa too showed a strong antitumor activity *in-vivo* (Im et al., 2005).

A. vera extract at the dose of 100 mg/kg was found to suppress delayed-type hypersensitivity reactions induced by SRBCs in mice. As shown by a marked increase in hemagglutination titers in mice was also detected. The study demonstrates that *A. vera* triggers both specific and non-specific reactions to a greater amount. The study included the acute toxicity and preliminary phytochemical screening of *A. vera.* From the outcomes found and phytochemical studies, the immunostimulant effect of *A. vera* could be attributed to the alkaloid content (Atul et al., 2011)**.**

6.3.11 CHRONIC AND DENTAL DISEASE

Choonhakarn et al. (2008) investigated the efficacy of *A. vera* gel in the treatment of oral lichen planus. Around 54 patients were randomized into 2 groups to obtain *A. vera* gel or placebo for 8 weeks. There were erosive and ulcerative lesions in 83% and 17%, correspondingly. The most shared site of oral lichen planus was the lower lip. Around 22 of 27 patients treated with *A. vera* (81%) had a decent response after 8 weeks of treatment, whereas 1 of 27 placebo-treated patients (4%) had a comparable response. Also, 2 patients treated with *A. vera* (7%) had a whole clinical decrease. Burning pain entirely vanished in 9 patients treated with *A. vera* (33%) and in 1 treated with a placebo (4%). Symptomatology enhanced through at the smallest 50% (respectable response) in 17 patients treated by *A. vera* (63%) and in 2 treated with a placebo (7%). Not at all thoughtful side-effects were found in both groups. So, it was concluded that the *A. vera* gel is statistically more expressive in effect than the placebo in persuading medical and symptomatological enhancement of oral lichen planus. Consequently, *A. vera* gel can be measured as a harmless treatment aimed at patients with oral lichen planus (Choonhakarn et al., 2008). Hayes (1999) also reported successful treatment of Lichen planus with *Aloe vera*.

Ipshita et al. (2018) explored the effectiveness of 1% Alendronate and *A. vera* gel as an adjunct to scaling and root planning in chronic periodontitis patients with class II furcation faults. The mean searching depth reduction and relative horizontal clinical attachment level and relative vertical clinical attachment level gains were greater in the Alendronate group than in the *A. vera* and placebo groups at 6 and 12 months. Moreover, an expressively greater mean percentage of defect depth reduction (DDR) was found in the Alendronate group than in the *A. vera* groups at 6 and 12 months, respectively. Alendronate showed important enhancement in all clinical parameters, along with superior DDR, compared to *A. vera* in the treatment of class II furcation defects as an adjunct to scaling and root planning (Ipshita et al., 2018). Jittapiromsak et al. (2010) reported that acemannan, an extracted product from *A. vera*, stimulates dental pulp cell proliferation, differentiation, mineralization, and dentin formation. The outcomes exposed that acemannan importantly augmented pulp cell proliferation, alkaline phosphatase (ALP) activity, bone morphogenetic protein-2, mineralization, dentin sialoprotein expression, etc., compared to an untreated group. The acemannan-treated group correspondingly showed the whole same calcified Dentin Bridge and decent pulp tissue organization, whereas neither was noticed in the calcium hydroxide-treated and sham groups. Acemannan too has pulpal biocompatibility and promotes soft tissue organization.

The efficiency of locally delivered 1% metformin and *A. vera* gel as an adjunct to scaling and root planning in the treatment of intrabony defects in chronic periodontitis patients were investigated by Kurian et al. (2018). Gingival index, pocket probing depth, bleeding on probing, and clinical attachment level enhanced in all the groups; but, the mean pocket probing depth reduction, clinical attachment level gain, and percentage of bone fill were found to be greater in the metformin and *A. vera* groups than the placebo group at altogether visits. So, the authors concluded that the local delivery of 1% metformin and *A. vera* gel stimulates a significant pocket probing depth reduction, clinical attachment level gain, and improved bone fill and regeneration when compared with placebo gel. Outcomes were suggestively better with the use of 1% metformin gel than with *A. vera* gel (Kurian et al., 2018).

Corticosteroids are supported for the treatment of oral lichen planus and have their individual side effects. Mansourian et al. (2011) compared the therapeutic effects of *A. vera* mouthwash with triamcinolone acetonide 0.1% on oral lichen planus. Baseline characteristics, as well as pain and burning sensation score, size, and clinical characteristics of the lesions rendering to Thongprasom index, were not dissimilar between the 2 treatment groups.

Both *A. vera* and triamcinolone acetonide suggestively condensed the visual analog scale score, Thongprasom score, and size of the lesions later in treatment and after 2 months of cessation of the treatment. In the *A. vera* group, 74% of patients, and in the triamcinolone acetonide group 78% of patients displayed some degree of healing in the last follow-up (Mansourian et al., 2011).

Gupta et al. (2014) investigated the antiplaque efficacy of *Aloe vera* mouthwash on a 4-day plaque re-growth model. The outcomes presented that *A. vera* mouth rinse is similar in the effect of reducing plaque as Chlorhexidine compared to placebo over a period of 4 days. There was a significant decrease in plaque in *A. vera* and chlorhexidine groups and no statistically important variance was detected among them. *A. vera* mouthwash revealed that there are no side effects.

Moghaddam et al. (2017) evaluated the effects of the local application of *A. vera* gel as an adjunct to scaling and root planning in the treatment of patients with chronic periodontitis. There was no important variance in plaque index in the three stages among the control and experimental groups. In total patients, there was an important enhancement in the 3 stages in the gingival index and probing depth for both experimental groups treated only with scaling and root planning or a combination of scaling and root planning and *A. vera*. This result showed that the local application of *A. vera* gel could be considered an adjunctive treatment by scaling and root planning for chronic periodontitis (Moghaddam et al., 2017).

Herbal agents such as *A. vera* have been used in therapeutic and dental treatment for thousands of years. Pradeep et al. (2016) studied the clinical efficiency of locally delivered *A. vera* gel used as an adjunct to scaling and root planning in the treatment of patients with type 2 diabetes mellitus and chronic periodontitis. Patients in the group treated with *A. vera* gel displayed significantly better mean decreases in plaque index, modified sulcus bleeding index, and probing depth and mean gain in clinical attachment level compared with those in the placebo group from baseline to 3 months. A gain in clinical attachment level was significantly greater in the treated group at all-time intermissions against group one. So, it was concluded that the adjunctive use of locally brought *A. vera* gel, in comparison to locally brought placebo gel, is connected with a greater decrease in plaque index, modified sulcus bleeding index, and probing depth as well as more gain in clinical attachment level in patients with type 2 diabetes mellitus and chronic periodontitis (Pradeep et al., 2016).

Yeturu et al. (2016) evaluated the effect of *A. vera*, chlorine dioxide, and chlorhexidine mouth rinses on plaque and gingivitis in orthodontic treatment. It was concluded that chlorine dioxide showed better results than others.

Various treatments have been used in application to indicative oral lichen planus with different outcomes which may be caused by the refractory nature of the disease. Salazar-Sanchez et al. (2010) evaluated the effectiveness of the topical application of *A. vera* in oral lichen planus likened to a placebo. No statistically important variations were noted between together groups relative to pain after 6 and 12 weeks. In the *A. vera* group, complete pain remission was attained in 31.2% of the cases after 6 weeks and in 61% after 12 weeks. In the placebo group, these fractions were 17.2% and 41.6%, respectively. There were no adverse effects in any of the groups. With respect to the excellence of life, important variations were detected between both the groups in the psychological disability domain and the total OHIP-49 score (Salazar-Sanchez et al., 2010).

Sholehvar et al. (2016) investigated the effect of *A. vera* gel on the viability of dental pulp stem cells. *A. vera* presented an important higher viability than Hank's balanced salt solution (HBSS) (74.74%). The 50% *A. vera* presented higher viability (97.73%) than other concentrations. PDT in 50% concentration was 35.1 h and for HBSS was 49.5 h. DPSCs were rod-shaped and were positive for CD73 and negative for CD34 and CD45 and Karyotyping was normal. *A. vera* as a cheap and obtainable herb can recover the existence of avulsed or broken teeth in emergency cases as a transfer media (Sholehvar et al., 2016).

Vangipuram et al. (2016) investigated the comparative efficacy of *A. vera* and Chlorhexidine mouthwash on Periodontal Health. There was an important decrease in the mean scores of completely the parameters with the *A. vera* and chlorhexidine group. Post hoc test displayed important variance in mean plaque and gingival index scores of *A. vera* and placebo and chlorhexidine and placebo group. No important variance was experiential between the *A. vera* and chlorhexidine groups. The authors concluded that the herbal product *A. vera* has revealed equal efficiency as Chlorhexidine (Vangipuram et al., 2016).

6.3.12 RADIOPROTECTIVE AND REPARATIVE EFFECTS

Nejaim et al. (2014) evaluated the radioprotective and reparative effects of compounds based on *A. vera*, zinc, and copper compared to salivary gland

dysfunction in rats. Rats that had been administered *A. vera* previously or afterward irradiation displayed a significantly higher salivary flow rate than rats that had been simply exposed. When both materials were administered, a statistically important variance in the salivary flow rate was detected in assessment with the radioactivity single group 7 days after irradiation. The result showed that *A. vera* has radioprotective material.

6.3.13 ANTITUMOR ACTIVITY

Antitumor activity of 50% ethanol extract (100 mg/kg) of *A. vera* was assessed in contradiction of Ehrlich ascites carcinoma (EAC) tumor in mice. *A. vera* displayed a reduction in stomach circumference and body weight of EAC tumor-bearing mice. Hematological profile returned towards normal levels in extract-treated mice. Treatment by *A. vera* restored the serum biochemical parameters to normal levels and reduced the levels of lipid peroxidation (LPO), and augmented the levels of condensed glutathione (GSH) and other antioxidant enzymes such as CAT, SOD, and GPx, etc. Around 50% ethanol extract of *A. vera* showed an antitumor effect by modulating LPO and augmenting the antioxidant defense system in EAC-bearing mice (Naveena et al., 2011).

6.3.14 ANTIOXIDANT ACTIVITY

The alcoholic extract of *A. vera* leaf skin was fractionated by liquid-liquid partition by using ethyl acetate (EA), hexane, butanol, and chloroform-ethanol. The total phenolic content of the 4 different fractions was determined by using the Folin-Ciocalteu method and their antioxidant activity which was essayed concluded some *in-vitro* methods, i.e., the antioxidant capacity by using the β-carotene bleaching method, phosphomolybdenum method, radical scavenging activity using DPPH assay and reducing power assay. The chloroform-alcohol fraction displayed the highest total phenolics, the highest scavenging activity, and the greatest plummeting power, followed by EA, butanol, and hexane extracts. Nevertheless, the hexane fraction presented the highest antioxidant capacity (471.300 ± 0.013) and the highest antioxidant activity coefficient by the β-carotene bleaching method (Miladi and Damak, 2008).

6.3.15 ANTI-ULCER ACTIVITY

Borra et al. (2011) determined the effects of *A. vera* on indomethacin-persuaded ulcers in rats. It was found that *A. vera* presented anti-ulcer activity comparable to the standard drug of omeprazole.

6.3.16 LIVER PROTECTION

Extracts of *A. vera* were tested for their hepatoprotective activity. Petroleum ether (PE) and chloroform extracts lacked hepatoprotective activity. The most active distilled water extract was studied in detail. Distilled water extract displayed important hepatoprotective activity in contradiction to CCl_4-induced hepatotoxicity. The hepatoprotective potential was inveterate by the restoration of LPO, glucose-6-phosphatase, GSH, microsomal aniline hydroxylase, and amidopyrine N-demethylase to nearby normal. Histopathology of the liver tissue supported the biochemical results confirming the hepatoprotective potential of distilled water extract. This showed that the aqueous extract of *A. vera* significantly accomplished restoring the integrity of hepatocytes, shown by improvement in physiological parameters, the excretory capacity of hepatocytes, and also by stimulation of bile flow secretion. Distilled water extract did not show any sign of toxicity up to oral at a dose of 2 g/kg in mice (Chandan et al., 2007).

6.3.17 COSMECEUTICAL POTENTIAL

A. vera gel is widely used in cosmetics and toiletries for its moisturizing and revitalizing action (Vogler and Ernst, 1999; West and Zhu, 2003). The whole leaf of *A. vera* is known to aid cellular repair as well as digestion, and assimilation of foods, vitamins, minerals, and other vital nutrients to rejuvenate the skin (Ramachandra and Ramachandra, 2008). Fresh gel, juice or formulated products have been used for medical and cosmetic purposes and to enhance general health (Chithra et al., 1998). The polysaccharide-rich composition of *A. vera* extracts (*A. barbadensis*), frequently used in beautifying or cosmetic preparations, may be due to the moisturizing properties of the product. Dal'Belo et al. (2006) assessed the effect of beautifying or cosmetic preparations containing different concentrations of freeze-dried *A. vera* extract on skin hydration, after a single and a 1 and 2-week period of application, by using skin bioengineering techniques. Constant formulations

containing 5% (w/w) of a trilaureth-4 phosphate-based blend were added with 0.10%, 0.25%, and 0.50% (w/w) of freeze-dried *A. vera* extract and applied to the volar forearm of 20 female subjects. The results showed that freeze-dried *A. vera* extract is a naturally effective component for improving skin hydration, may be through a humectant mechanism. It may be used in moisturizing, beautifying, or cosmetic preparations and the treatment of dry skin (Dal'Belo et al., 2006).

A. vera is a natural product that is now regularly used in cosmetics. However, there are numerous suggestions for its use; advanced trials are required to regulate its real efficiency (Surjushe et al., 2008).

KEYWORDS

- ***Aloe vera***
- **antifungal creams**
- **cosmoceutical**
- **polyacrylamide gel electrophoresis**
- **polysaccharide**
- **therapeutic plants**

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CHAPTER 7

Bioactives and Pharmacology of *Anogeissus latifolia* (Roxb. ex DC.) Wall. ex Bedd.

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7.1 INTRODUCTION

Anogeissus latifolia (Roxb. ex DC.) Wall. ex Bedd. (Combretaceae) is a tree that ranges in size from medium to large, and is found in dry deciduous forests, native to India, Myanmar, Nepal, and Sri Lanka. Leaves are opposite or sub-opposite. The bark is smooth and gray-white in color exfoliating in irregular thin scales. Flowers are sessile and arranged in dense heads. The fruit is thin and compressed with a beak, and the seed is ovoid. In the months of September to March, trees produce flowers and fruits.

The plant is used in the Ayurvedic medical system. Traditionally, a range of illnesses has been treated with the bark, including skin diseases (Roy and Chaturvedi, 1986), snake bite and scorpion stings (Mishra and Billore, 1983), stomach diseases (Jain et al., 1970), colic (Apparanantham and Chelladurai, 1986), wounds, diabetes, inflammation (Seth and Sharma, 2004), cough (Balla et al., 1982) and diarrhea (Ramachandran et al., 1981).

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7.2 BIOACTIVES

Preliminary phytochemical analysis of *A. latifolia* in methanolic extract divulges the presence of terpenoids, phenols, alkaloids, flavonoids, glycosides, flavanols, and saponins. The concentrations of secondary metabolites in the apical stem bark were found to be higher than in the inner and mature outer stem bark (Patil and Gaikwad, 2010). While putting some extra insight into a range of secondary metabolites, Sharma et al. (2020) revealed the occurrence of novel compounds like carbohydrates, steroids, quinones, furanoids, and triterpenoids. The estimated total phenolic content and flavonoid content were 62.86 mg gallic acid equivalent (GAE) and 40.64 mg quercetin equivalent per gram of *A. latifolia* ethanolic extract, respectively (Sharma et al., 2020).

Deshapande et al., in 1976 isolated 3,3'-di-O-methyle ellagic acid, 4'-β-D-Xyloside and 3,4,3'-tri-O-methylflavellagic acid, 4'-D-glucoside derived from stem bark from the ethyl acetate (EA) fractions of *A. latifolia* stem bark, a steroid, β-Sitosterol, and a triterpenoid, 3-hydroxy-28-acetytaraxaren were isolated (Rahman et al., 2007). For the simultaneous quantification of two physiologically active flavonoids, i.e., quercetin, and rutin in bark using HPTLC, a quick and easy approach was established. The separation was performed using thin-layer chromatography. While Govindarajan et al. (2005) isolated three major tannoid principles which support the reports by bioassay-guided isolation. Effective antioxidant activity was found in the EA and butanol fractions. The isolation of ellagic acid was aided by bioassay-guided isolation and the most active components were gallic acid and dimethyl ellagic acid, both of which were determined using HPLC. A compound from the class tannin was isolated from *A. latifolia* by Reddy et al. (1964). Analysis and other degradative research on gallotannin revealed that it is an octa- or nonagalloylated glucose. Hydrolysis of alkali studies is used to determine the glucose core of the tannin. It was also discovered that the tannin includes β-penta-O-galloylated glucose that is connected to chains with at least three galloyl groups through methanolysis and other processes. *A. latifolia* reflects a diverse range of biologically active chemical constituents stated in Figure 7.1.

7.3 PHARMACOLOGY

7.3.1 ANTIULCER ACTIVITY

A. latifolia bark can be justified for antiulcer activity due to the presence of a high quantity of gallic acid and ellagic acid (0.95% w/w and 0.25% w/w, respectively) in the extract (200 mg/kg). These components protect

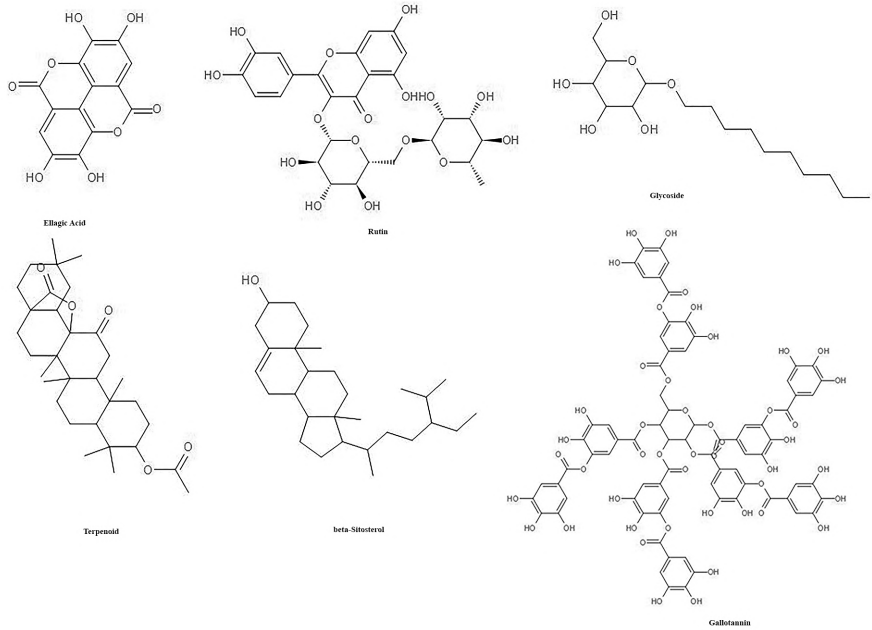


FIGURE 7.1 Chemical compounds present in Anogeissus latifolia.

aspirin-induced ulcers in gastric mucosa by 66%. This protection might be possible due to its 5-lipoxygenase inhibitory effect (Govindarajan, 2004a). Extract produces a gastroprotective effect on ethanol-induced ulcers in an as dose-dependent manner. *A. latifolia* extract is also active against the cold resistant stress-induced ulcers (84.16%) and pylorus ligation (67.64%) at 200 mg/kg may be due to its histamine antagonistic, anticholinergic, antisecretory, and antioxidant effect (Govindarajan, 2004b).

7.3.2 ANTIMICROBIAL ACTIVITY

Rahman et al. (2007) examined the antimicrobial activity of EA and methanol extracts of *A. latifolia* which indicated substantial inhibitory activity against microbial growth which could be possibly due to the presence of compounds like 3-ß-hydroxy-28-acetyltaraxaren and ß-sitosterol. Moreover, a wide range of bacteria – three Gram + bacteria *Bacillus subtilis, Micrococcus* sp., as well as five Gram – bacteria *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Salmonella typhi,* were tested for antimicrobial activity, where *Salmonella typhi* was found to be the most susceptible of all the bacteria studied (Patil and Gaikwad, 2010).

7.3.3 ANTIOXIDANT POTENTIAL

Govindrajan (2004b) tested the antioxidant ability of a 50% ethanolic extract of *A. latifolia* and found dose-dependent inhibition of nitric oxide (NO), DPPH radical, hydrogen peroxide (H_2O_2), and superoxide radicals. The percentage of gallic acid in the bark ascertains that the antioxidant activity may be due to the same. *A. latifolia* extract has potent antioxidant activity, achieved by scavenging abilities observed against DPPH, and lipid peroxidation (LPO). It showed high-H donating ability shown by the scavenging of DPPH radical (Govindrajan et al., 2004b).

7.3.4 WOUND HEALING POTENTIAL

By reducing the wound's surface area and raising its tensile strength, *A. latifolia* speeds up the recovery process. For complete epithelization *A. latifolia*, took only 15 days. The healed area and the hydroxyproline level were both measured and found to be in accord (Govindaranjan et al., 2004a).

7.3.5 HEPATOPROTECTIVE ACTIVITY

A. latifolia was investigated for hepatoprotective activity against CCl_4-induced hepatotoxicity in primary hepatocyte monolayer cultures *in vitro*. In the CCl_4-damaged primary monolayer community, a protective behavior was observed. In rats with CCl_4-induced liver damage, a hydroalcoholic extract of *A. latifolia* (300 mg/kg) was found to have protective activity as measured by serum marker enzyme activity. Moreover, the findings lead to the conclusion that the hydroalcoholic extract of *A. latifolia* is hepatoprotective. As a result, the use of this plant in liver disease management is recommended (Pradeep et al., 2009).

7.3.6 DIURETIC ACTIVITY

Employing an in-vivo Lipschitz test technique, the diuretic capacity of a leaf (methanol and aqueous extracts) was tested in albino rats. For the study, the parameters taken were: (a) urine volumes; and (b) urinary sodium and potassium ion concentrations. In the case of the study, Furosemide was used as the standard. When compared to control methanol and aqueous extract at 500 mg/kg indicated that body weight had effectively increased urine volume and electrolyte excretion. Both extracts showed significant diuretic activity (Hemamalini et al., 2011).

7.3.7 ANTICANCER ACTIVITY

Diab et al. (2006) designed and evaluated an experiment for *in vitro* anti-proliferative potential of *A. latifolia.* SRB and MTT assays were used to assess cytotoxicity in human cancer cell lines, including (i) lung (A549); (ii) prostate (PC-3); (iii) breast (T47D and MCF-7); (iv) colon (HCT-16 and Colo-205); and (v) leukemia (THP-1, HL-60, and K562). The researchers discovered that leaf extract suppressed the proliferation of nine human cancer cell lines in a concentration-dependent way. By preventing the G0/G1 phase, the extracts reduced the leukemia HL-60 and K562 cell viability. The researchers discovered that the plant extracts for nine human cancer cell lines were anti-proliferative in a concentration-dependent manner of the cell cycle. *Areca catechu* extract at 100 g/mL triggered G2/M arrest in K562 cells, which was unexpected. HL-60 cells were incubated with these extracts for 24 hours. DNA fragmentation analysis showed a cell necrosis smear pattern on agarose gels (Diab et al., 2006).

7.3.8 ANTHELMINTIC ACTIVITY

A. latifolia possesses potent anthelmintic activity in chloroform (bark) and petroleum extract (leaf) which was proved by Parvathi et al. (2009a) by demonstrating efficacy for the parameters examined. Several extracts from the bark and leaves of *A. latifolia*, such as petroleum ether (PE), chloroform, and methanol, were tested for anthelmintic activity against earthworms, *Pheritima posthuma*. An assay was performed to determine the time of paralysis and death of the worm at five different doses (10, 20, 30, 40, and 50 mg/ml) of each extract. All of the extracts had an anthelmintic activity that ranged from mild to effective. PE leaf extracts and chloroform bark extract have the most effective anthelmintic action when compared to the other extracts. The results were compared to those of the standard medication albendazole (Parvathi et al., 2009).

7.3.9 ANTIDIABETIC ACTIVITY

Aqueous extract of *A. latifolia* bark possesses significant antidiabetic properties. Streptozotocin-nicotinamide (STZ-NIN)-induced type 2 diabetic rats were treated with *A. latifolia* bark (AEALB). In this place, rats were given a 2 g/kg dose of AEALB to test its acute toxicity. STZ-NIN (65 mg/

kg–110 mg/kg, i.p.) was given to rats to cause type 2 diabetes. The diabetic rats were given an oral dose of AEALB 100 and 200 mg/kg for four weeks. In diabetic rats treated with both doses of AEALB, increased body weight, hemoglobin, reduced blood glucose, glycosylated hemoglobin, and other biochemical parameters were observed compared to diabetic control rats. When diabetic rats were given AEALB, their lipid profiles and antioxidant levels were restored to near-normal levels, compared to diabetic control rats (Ramachandran et al., 2012). Moreover, Vyas et al. (2019) experimented with and established a benchmark for the future use of this *A. latifolia* as a diabetes drug scientifically. The study reflected that hydro-alcoholic extract from the bark of *A. latifolia* 300 mg/kg (ALBE-II) showed significant hypoglycemic activity as compared to glibenclamide and the diabetic group. The bark extract does not exhibit significant diuretic activity which is considered a positive marker in diabetic phenomena. Hence the findings support that the extract of *A. latifolia* possesses antidiabetic activity (Vyas et al., 2019).

7.3.10 ANTILYPOLIPIDEMIC ACTIVITY

In albino rats, Parvathi et al. (2009b) investigated the hypolipidemic potential of *A. latifolia* in terms of serum lipid levels. In hyperlipidemic-induced rats, treatment with gum ghatti decreased total cholesterol and triglyceride levels by 500 mg and 750 mg/kg of body weight, respectively, and increased high-density lipoprotein cholesterol by 750 mg/kg of body weight.

KEYWORDS

- ***Anogeissus latifolia***
- **antilypolipidemic activity**
- **antiulcer activity**
- **diabetic phenomena**
- **glibenclamide**
- ***Pheritima posthuma***
- **streptozotocin**

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CHAPTER 8

A Review on Phytochemistry and Pharmacology of *Calophyllum inophyllum* L.

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8.1 INTRODUCTION

Calophyllum inophyllum L. (synonyms: *Balsaminaria inophyllum* (L.) Lour., *Calophyllum blumei* Wight, *Calophyllum bitangor* Roxb.), belonging to the family Clusiaceae, is a woody species indigenous to Australia, East Africa, Southern coastal India and Malaysia (Stephens, 1980). The tree is commonly called Alexandrian-laurel, Indian-Laurel, ball nut tree or beauty leaf (English), Sultan Champa (Hindi), and Punna (Malayalam) (Susanto et al., 2019). It is grown as an evergreen tree, famous for avenue planting, and grows up to 20 m in height with a broad canopy of irregular branches (Hathurusingha and Ashwath, 2011). The tree is adapted to maritime, littoral, and riparian regions in warm tropics and sub-tropics and is also tolerant of saline soils.

C. inophyllum is a slow-growing branching tree with a broad canopy of glossy elliptical leaves. Leaves are simple, opposite, obovate-elliptic lamina having 10–20 cm long and 6–9 cm width, glabrous, rounded or cuneate base, rounded leaf apex, parallel lateral veins perpendicular prominent midrib and entire leaf margin (Susanto et al., 2017). Trees start to produce flowers after 6–7 years old and usually flower twice a year, in late spring and late autumn. Flowers are white, and bisexual, and are usually produced in terminal or axillary panicles of 4–15 flowers. Fruits is an indehiscent greenish globose or subglobose drupe measuring 2.5–4.0 cm in diameter. The outer greenish

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skin becomes wrinkled and the color turns yellow to brown at the time of maturity. *C. inophyllum* is a significant timber-yielding tree with several medicinal properties instead of its rarely eaten fruit. A brief literature survey reveals that there is no nutritive information regarding its fruit.

C. inophyllum plant has many traditional and therapeutic properties that can be utilized by humans (Go´mez-Verjan et al., 2015). All parts of this tree contain several bioactive compounds. The fruit oil is extensively used against rheumatism, gonorrhea, and itching (Gupta and Gupta, 2020). Fruit shell was too utilized for the generation of pyrolytic oil. Fruit shell was also used for the production of pyrolytic oil (Alagu et al., 2015). In the pharmaceutical industry, bioactives from the tree act as a potent antibacterial, antiviral, disinfectant, antineoplastic, antiseptic, diuretic, and purgative agents (Potti and Kurup, 1970; Hathurusingha and Ashwath, 2011; Gómez-Verjan et al., 2015). The tree bark has been used in Indo-Chinese medicine for orchitis (Dweck and Meadows, 2002) and is also used to cure hemorrhages and ulcers. The bark extract contains cytotoxin calocoumarin which can act as an anticancer agent (Itoigawa et al., 2001). Traditional practitioners rubbed the latex obtained from *C. inophyllum* on the skin to cure rheumatoid arthritis and psoriasis (Gupta and Gupta, 2020). Root decoction is used in the treatment of leprosy and leaf decoction in the treatment of eye diseases.

C. inophyllum is valued in various traditional folk medicine practices in different continents in Asia and the Pacific Islands make utilize this plant in the treatments of sexually transmitted diseases, hypertension, rheumatoid arthritis, eye illness, hemorrhoids, varicose veins, chronic ulcers and skin infections (Chuah et al., 2007; Dweck and Meadows, 2002; Su et al., 2008).

8.2 PHYTOCHEMICAL CONSTITUENTS

Calophyllum inophyllum is a wealthy source of bioactive compounds such as coumarins, xanthones, pyranochromanone, flavonoids, glycosides, and triterpenes. These compounds exhibited biological properties such as anticancer, antimicrobial, antinociceptive, inhibition of P glycoproteins, inhibition of sulfotranferases, selective inhibition of HIV-1 reverse transcriptase activity, molluscicidal, antisecretory, and cytoprotective (Su et al., 2008). Gómez-Verjan et al. (2015) reviewed that the root extract of *C. inophyllum* contains major compounds such as inophyllin A, caloxanthone A, and B, 1,5-dihydroxyxanthone-6-desoxijacarubin, inophyllum, isoinophyllum. Moreover, the compounds namely amentoflavone, friedelin, calofoloid, epicatechin, apetatolide, stigmasterol phenolic cinnamic acid, coumarins

such as 4-phenylcoumarins inophyllum A, C, D, and E and three tricyclic coumarins such as calocoumarin A, B, and C, also separated from the root extracts. The study conducted by Yimdjo et al. (2004) found that the nut and root bark of *C. inophyllum* contains xanthones, coumarins, brasiliensic acid, inophylloidic acid, calophyllolide, friedelan-3-one, inophyllum C, and E and also reported the isolation and characterization of a xanthone derivative (inoxanthone). Ee et al. (2009) reported the following six xanthones such as brasilixanthone, 1,3,5-trihydroxy-2-methoxy xanthone, caloxanthone A, pyranojacareubin, caloxanthone B and tovopyrifolin yielded from the root bark of *C. inophyllum*. Triterpene (friedelin) and triterpenoid (b-sitosterol) have also been isolated from root bark (Ee et al., 2004, 2006).

Al-Jeboury and Locksley (1971) found out jacareubin, euxanthone, 1,5,6-trihydroxyxanthone, buchanaxanthone, 6-desoxyjacareubin, 2-(3,3-dimethylallyl)-1,3,5-trihydroxyxanthone and 2-(3,3-dimethylallyl)-1,3,5,6-tetrahydroxyxanthone from heart wood of *C. inophyllum*. Goh and Jantan (1991) also identified various xanthones viz; 2-(3-hydroxy-3-methylbutyl)-1,3,5,6-tetrahydroxyxanthone, 2-(3-methylbut-2-enyl)-1,3,5,6-tetrahydroxyxanthone and 2-(3-methylbut-2-enyl)-1,3,5-trihydroxyxanthone from heart wood. In addition to reported xanthones, sapwood contains erythrodiol acetate, friedelin, friedelan-3-ol, and γ-silosterol (Daniel, 2006).

Li et al. (2009) isolated a new xanthone namely inophyxanthone A [1,3,5-trihydroxy-2-(1,1-dimethylallyl) xanthone] and four known xanthones such as gerontoxanthone B, jacareubinpancixanthone A, and pyranojacareubin from *C. inophyllum* leaves. Laure et al. (2005) isolated three new friedelane-type triterpenoids (3,4-secofriedelan-3,28-dioic acid, 27-hydroxyacetate canophyllic acid, 3-oxo-27-hydroxyacetate friedelan-28-oic acid) from the leaves of *C. inophyllum*. Inophyllums B, C, G_1, G_2, and P, pyranocoumarins, and calophyllolide were also isolated and determined from leaves of *C. inophyllum* by using an HPLC–UV-diode array detection technique (Laure et al., 2008). The following compounds such as 2-hydroxyxanthone, 4-hydroxyxanthone, 1,7-dihydroxyxanthone, 1,3,5-trihydroxy-2-methoxyxanthone, and 6-deoxyjacareubin were first isolated from leaves and stem of *C. inophyllum* (Li et al., 2007). Ali et al. (1999) reported that the ethanolic leaves extract of *C. inophyllum* yielded inophynone and isoinophynone. Patil et al. (1993) isolated calophyllic acid and isocalophyllic acid from the leaves of *C. inophyllum*.

The major active constituents of the fruits include xanthones (dihydroxy-6-methoxyxanthone) and inophyllums (inophyllum A, C, and E) (Zakaria et al., 2014). Inocalophyllin A and B along with their methyl esters were also isolated

from the seeds of *C. inophyllum* (Shen et al., 2003). Haerani et al. (2021) isolated two new xanthones namely 1,3,6,7-tetrahydroxy-5-methoxy-4-(1′,1′-dimethyl-2′-propenyl)-8-(3″,3″-dimethyl-2″-propenyl)-xanthone and (2′S)-7-hydroxy caloxanthone B from the root of *C. inophyllum*. The stem bark of *C. inophyllum* yields Brasixanthone B (Mah et al., 2015), and the male reproductive part of the flower yields quercetin and myricetin (Subramanian and Nair, 1971).

8.3 PHARMACOLOGICAL IMPORTANCE

The pharmacological importance of *C. inophyllum* was known from 1970 to till the date due to its biologically active compounds, especially xanthones and coumarins. The plant has been well recognized in modern pharmacopeia due to its active constituents exhibiting anti-HIV, anti-cancer, and anti-parasitic activities. In addition, the seeds of *C. inophyllum* are a well-known source of biodiesel.

8.3.1 ANTIVIRAL ACTIVITY

Many pyranocoumarins, calophyllolide, inophyllums B, C, G(1), G(2), and P from leaves of *C. inophyllum* were found to inhibit HIV-1 (Patil et al., 1993; Laure et al., 2008). Inophyllums isolated from *C. inophyllum* acts as inhibitors of human immunodeficiency virus (HIV) type 1 reverse transcriptase (Taylor et al., 1994; De Clercq, 2000; Lim and Lemmens, 2012). The seeds of *C. inophyllum* were additionally found to contain many illustrious coumarins, among that costatolide and inophyllum were the potent HIV reverse transcriptase inhibitors (Spino et al., 1998). Thus *C. inophyllum* with success is used as a plant supply for the anti-HIV drug. Gómez-Verjan et al. (2015) revealed that coumarins and xanthones isolated from *C. inophyllum* are effective in the treatment of leukemia. Jantan et al. (2001) studied platelet-activating factor (1-alkyl-2-acetyl-glycero-3-phosphocholine) receptor binding inhibitory effects utilizing rabbit platelets, the study found that the three isolated compounds from *C. inophyllum* namely 6-deoxyjacareubin, 2-(methylbut-2-enyl)-1,3,5-trihydoxyxanthone and 2-(3-methylbut-2-enyl)-1,3,5,6-tetrahydroxyxanthone inhibited binding of platelet-activating factor to rabbit platelet.

8.3.2 ANTIMICROBIAL ACTIVITY

C. inophyllum oil exhibits antibacterial activity against many Gram-positive bacteria (Bhat et al., 1954). Active compounds such as friedelin, canophyllol,

canophyllic acid, and inophynone of *C. inophyllum* seed oil exhibit antibacterial and antifungal properties (Sundaram et al., 1986; Mahmud et al., 1998). Mahmud et al. (1998) also proved that xanthones and coumarins in seed oil precisely prevent lipid peroxidation (LPO). Yimdjo et al. (2004) evaluated the anti-microbial and antioxidant properties of xanthones, coumarins, brasiliensic acid, inophylloidic acid, calophyllolide, friedelan-3-one, inophyllum C, and E and a xanthone derivative (inoxanthone). Potti and Kurup (1970) reported the isolation of greenish yellow semi-solid principle ($C_{32}H_{46}O_6$) from the root bark of *C. inophyllum* that was active against many gram-positive bacteria and activity is enhanced by phosphate, but not by vitamins, amino acids, or thiol reagents.

8.3.3 ANTICANCER ACTIVITY

Among 10 4-phenylcoumarins isolated from *C. inophyllum,* calocoumarin-A exhibited more inhibitory activity against the Epstein-Barr virus (Itoigawa et al., 2001). Li et al. (2010) reported that a new friedelane-type triterpene (3 b, 23-epoxy-friedelan-28-oic acid) and triterpenoids such as friedelin, epifriedelanol, canophyllal, canophyllol, canophyllic acid, 3-oxo-friedelan 28-oic acid, and oleanolic acid, isolated from *C. inophyllum,* exhibited growth inhibition on human leukemia cells (HL-60).

A new prenylated xanthone caloxanthone N and gerontoxanthone C were isolated from the ethanolic extract of the twigs of *C. inophyllum* and showed cytotoxicity against chronic myelogenous leukemia cell line (K562) (Xiao et al., 2008) and prenylated xanthone caloxanthone O from the ethanolic extract of the twigs of *C. inophyllum* showed cytotoxicity against human gastric cancer cell line (SGC-7901) (Dai et al., 2010).

8.3.4 WOUND HEALING ACTIVITY

Lactone and calophyllic acid obtained from *C. inophyllum* act as antibiotic agents which contributed to the oil's amazing cicatrizing power (Dweck, 2003). *C. inophyllum* oil showed wound-healing properties and was used in formulating regenerative ointments.

8.3.5 ANTIULCER ACTIVITY

In rats, isolated xanthones (Jacareubin and 6-desoxy jacareubin) from *C. inophyllum* showed antiulcer activity (Gopalakrishnan et al., 1980).

8.3.6 ANTI-INFLAMMATORY ACTIVITY

4-phenyl coumarin calophyllolide exhibited significant anti-inflammatory activity (Bhalla et al., 1980). A nonsteroidal calophyllolide act as an anti-inflammatory agent and is effective against the increased capillary permeability in mice (Saxena et al., 1982).

8.3.7 ANTIOXIDANT ACTIVITY

Calanolide D and 12-oxocalanolide A, first identified from ethanol fraction of *C. inophyllum* oil, showed antioxidant properties (Cassien, 2021). Its cytoprotective properties and antioxidant properties make it a widely accepted natural UV filter in the preparation of ophthalmic solutions (Said et al., 2006).

8.3.8 MOLLUSCICIDAL ACTIVITY AND FLY REPELLENT ACTIVITY

Crude seed extract obtained from *C. inophyllum* exhibit molluscicidal properties, coumarin derivative 5,7-dihydroxy-6-(2-methylbutyryl)-4-phenylcoumarin exhibit molluscicidal activity (Ravelonjato et al., 1992). In humans, *C. inophyllum* seed oil (protection time, 0.56 h) is successful in repellency test against *Stomoxys calcitrans* (stable fly) (Hieu et al., 2010b). Another study indicates that *C. inophyllum* nut oil mixture formulated with steam-distillated pericarp of *Zanthoxylum piperitum* or seed oil of *Zanthoxylum armatum* were useful as potential repellents for stable fly (Hieu et al., 2010a).

KEYWORDS

- **anti-inflammatory activity**
- ***Calophyllum inophyllum***
- **fly repellent activity**
- **human immunodeficiency virus**
- **molluscicidal activity**
- **phytochemistry**
- **platelet-activating factor**

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CHAPTER 9

Phytochemical and Pharmacological Potential of Hard Milkwood, *Alstonia macrophylla* Wall. ex G. Don

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9.1 INTRODUCTION

Alstonia macrophylla Wall. ex G. Don (Family – Apocynaceae) is an evergreen tropical tree, native to South and Southeast Asia. The different plant parts are used for an extensive spectrum of ailments in traditional medicinal systems in China, India, Thailand, Malaysia, the Philippines, Africa, and Australia (Khyade et al., 2014). The leaves are in whorls of 3, oblong-obovate, 10–30 cm long, 5–7 cm extensive, pointed at both ends, and small stalked. The flowers are yellowish-white and borne on short cymes at the end of branches. The fruit is a 2-follicle, slender, 20–40 cm long. The seeds are small, flat, color deep-brown, especially along the edges.

A. scholaris and *A. macrophylla* are two vital medicinal plant species. In India, *Alstonia macrophylla* is used as another source for *Alstonia scholaris* in several herbal pharmacological preparations. Both are highly medicinal plants used in different traditional medicine. The leaves decoction and stem bark of *A. macropylla* are widely used in stomach ache, skin diseases, and urinary infections (Bhargava, 1983). The leaves are known to have anticholeric and high vulnerary effects and are greased with hot coconut oil for bruises, sprains, and disrupted joints as dressing and useful as febrifuge (Asolkar et al., 1992). Moreover, the leaf vapors are also inhaled in fever by

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the tribal community – of Shompen in the Nicobar Islands (Sharief and Rao, 2007; Kumar et al., 2008).

9.2 PHYTOCHEMISTRY

A total of 17 alkaloids, including six macro-lines (containing alstofolinine-A, a macro-line indole including a butyrolactone ring-E), two ajmaline, one sarpagine, and eight akuammiline alkaloids were sequestered from the leaf and stem-bark extracts of the Malayan *A. macrophylla* (Lim et al., 2014).

The phytochemical investigation of leaf crude extract discovered the occurrence of tannin, flavonoid, triterpenoid, alkaloid, sterol, and reducing sugars. More fractionation and purification of the n-butanol part of methanol solvent extract produced fraction-A, fraction-B, and fraction-C along with a few minor fatty acids as the major compounds (Chattopadhyay et al., 2004). In the *A. macrophylla* plant, the presence of steroids, lipids, saponin, tannin, alkaloids, flavonoid, phenol, and some other chemical components were recorded (Khyade and Vaikos, 2009). The three new picraline-type alkaloids namely alstiphyllanines E-G and new ajmaline-type alkaloid, *i.e.*, alstiphyllanine-H were sequestered from the leaf of *A. macrophylla* together with different 16 correlated alkaloids. Alstiphyllanines-E and alstiphyllanines-F presented reasonable Na (+)-glucose cotransporter (SGLT1 and SGLT2) inhibitory activity. Therefore, alstiphyllanines-E–H, picraline, and ajmaline-type alkaloids from *A. macrophylla* exhibited sodium-glucose cotransporter (SGLT1 and SGLT2) inhibitory activity (Arai et al., 2010). Around four new linearly attached bisindole alkaloids, lumutinines A–D, were sequestered from the stem-bark extract of *A. macrophylla* (Lim et al., 2011).

Hard milkwood bark methanol and dimethyl sulfoxide extract studied and resulted in the documentation of different 17 phytoconstituents, mainly alkaloids such as alstonerine 34.38%; strictamin 5.23%; rauvomitin 4.29% brucine 3.66%, etc., and triterpenoids namely γ-sitosterol 3.85%; lupeol 3.00%; 24-methylenecycloartanol 2.81%; campesterol 2.71%; β-amyrin 2.30%, stigmasterol 2.13%, etc. (Tan et al., 2019). Phytochemical study of an alkaloidal extract of *Alstonia macrophylla* bark led to the separation and documentation of 2 new nitrogenous products, alstoniaphyllines-A(1) and alstoniaphyllines-B(2), a new indole alkaloid, alstoniaphylline-C, and 8 known alkaloids. Alstonisine exhibited antiplasmodial activity against *Plasmodium falciparum* (Cheenpracha et al., 2013). GC-MS chromatogram discovered that around 30 identified components are present in this extract.

The flower extract of *A. macrophylla* indicated more amount of compounds *viz*. cycloartenol acetate (17.11%); 5H-1-pyrindine (12.44%); lupeyl acetate (10.12%); oleic acid (6.08%); benzenesulfonic acid, 4-hydroxy (4.25%); p-n-amylphenol (4.23%); and 4-methylindole (4.22%) (Andila et al., 2019).

The three new indole alkaloids *viz*. alstonamide, demethoxyalstonamide, and alstoumerine were sequestered from the leaf of *A. macrophylla*. The 1st two alkaloids are of the vincorine type and the last one is of the sarpagine type (Atta-Ur-Rahman et al., 1991). A new oxindole alkaloid, 16-hydroxy-N_b-demethylalstophylline oxindole has been sequestered from the leaf of *A. macrophylla* and N_a-methyl-1,2-dihydrostrictamine has also been isolated from this new source (Atta-Ur-Rahman et al., 1988). Oxindole alkaloid, N_b-demethylalstophylline oxindole has been sequestered from the leaf of *A. macrophylla* (Atta-Ur-Rahman et al., 1987). Four new alkaloids namely alstiphyllanines A–D (1–4), were isolated from *A. macrophylla*, and their chemical structures were determined by MS and 2D NMR analyses (Hirasawa et al., 2009).

The 10 new indole alkaloids *viz*. 10,11-dimethoxynareline, alstomaline, alstomicine, alstohentine, 16-hydroxyalstonal, 16-hydroxyalstonisine, 16-hydroxy-N(4)-alstophyllal, demethylalstophyllal oxindole, 6-oxoalstophylline, and 6-oxoalstophyllal were found from the Malayan *A. macrophylla* leaves extract (Kam and Choo, 2004). Three new indole alkaloids namely 10-methoxyaffinisine, 10-methoxycathafoline, and alstonerinal; In addition to alstonisine, alstonerine, alstophylline, vincamajine, alstonal, lochnerine, and cathafoline were also sequestered from the stem-bark extract of *A. macrophylla* (Kam et al., 1999). A new flavonoidic glycoside namely tricin-4′-O-β-l-arabinoside was sequestered from the leaf of *A. macrophylla* along with two known flavonoids, i.e., vitexin, and myricetin-3′-rhamnoside-3-O-galactoside (Parveen et al., 2010).

The three major phyto-compounds were sequestered from the polar fractions of the methanol extracts of *A. macrophylla* leaves such as β-sitosterol (fraction-A), ursolic acid (fraction-B), and β-sitosterol β-D-glucoside (fraction-C) along with less fraction which contains alkaloid and fatty acids (Arunachalam et al., 2009). The four different phyto-constituents namely a bisindole alkaloid, macralstonine, a new bisindole alkaloid, thungfaine, a secoiridoid glycoside, sweroside, and a new secoiridoid glycoside, naresuanoside were isolated from *A. macrophylla* stems ethanolic extract (Changwichit et al., 2011). The new two bisindole alkaloids *viz.* alstomacrophylline and alstomacroline, have been sequestered from the root bark of *A. macrophylla*, and other six known alkaloids *viz*. alstonerine,

macrocarpamine, alstophylline, 20-epi-antirhine, alstoumerine, and villastonine N-oxide. The monomeric indole alkaloid, 20-epi-antirhine has been sequestered for the first time from *A. macrophylla* (Keawpradub and Houghton, 1997).

9.3 PHARMACOLOGY

9.3.1 ANTI-MICROBIAL ACTIVITY

The methanolic crude and methanol–aqueous extracts of *A. macrophylla* leaf and the n-butanol part of the crude extracts revealed anti-microbial activity contrary to many strains of *Staphylococcus aureus, S. saprophyticus, S. faecalis, Proteus mirabilis, Escherichia coli, Microsporum gypseum, Trichophyton rubrum,* and *T. mentagrophytes* var. *mentagrophytes*. The minimum inhibitory concentration (MIC) values reached 64 to 1,000 µg/ml for bacteria and 32–128 mg/ml for dermatophytes. Moreover, the strains of *Pseudomonas aeruginosa*, *Klebsiella* sp., and *Vibrio cholera*e showed resistance in contradiction of and a semi-synthetic bisindole O-acetylmacralstonine have *in-vitro* treatment of the extracts up to 2,000 µg/ml concentration, while the 2 yeast species were resistant even at 128 mg/ml concentration (Chattopadhyay et al., 2001). A new flavonoidic glycoside, tricin-4'-*O*-β-L-arabinoside was sequestered from the leaf of *Alstonia macrophylla* and caused significant growth inhibition for *S. aureus, E. coli,* and *Salmonella typhimurium*. This compound was tested and confirmed for its anti-microbial activities (Parveen et al., 2010).

9.3.2 ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY

A study of crude leaf extract of *A. macrophylla* and *Mallotus peltatus* leaves showed potential analgesic and anti-inflammatory activity, which appears to be present due to the action of either ursolic acid (fraction B of *A. macrophylla* and fraction A of *Mallotus peltatus*) alone or the combination of all the fractions. However, to know the exact mechanism of its analgesic and anti-inflammatory activity further investigation of the purified compound is required (Chattopadhyay et al., 2005b).

9.3.3 ANTI-CANCER ACTIVITY

Root barks of *A. macrophylla* ethanolic extract from Thailand, have been evaluated for cytotoxic activity contrary to 2 human lung cancer cell lines, MOR-P (adenocarcinoma) and COR-L23 (large cell carcinoma) by using the SRB assay. Significant cytotoxic activity was shown by the extract of *A. macrophylla* on both cell lines (Keawpradub et al., 1997). The cytotoxicity of the ZnO NPs using *A. macrophylla* leaves extract, with numerous concentrations (1–100 μg/mL) was slow in human cancer cell lines such as MCF-7 (breast cancer), HepG2 (liver cancer) and A-549 (human lung alveolar epithelial) cells. After the experiment, several cytotoxicity assays, and cellular morphology investigation indicated that the cancer cell capability reduced with increasing ZnO NP concentration (Al-Ajmi et al., 2018).

A. macrophylla stems ethanolic extract showed an important inhibitory effect on acetylcholinesterase (AChE) measured by using Ellman assay. The four different phyto-constitutes were sequestered namely bisindole alkaloid, macralstonine; new bisindole alkaloid, thungfaine; a secoiridoid glycoside, sweroside, and a new secoiridoid glycoside, naresuanoside. Compound 4 showed moderate AChE and butyrylcholinesterase (BChE) inhibitory effects. Fascinatingly, this compound 4 inhibited cell growth in the human androgen-sensitive prostate cancer cell line (LNCaP) but do not affect the feasibility of human foreskin (HF) fibroblast cells (Changwichit et al., 2011).

From the root bark of *A. macrophylla,* 13 indole alkaloids sequestered and a semi-synthetic bisindole O-acetylmacralstonine have been assessed for cytotoxic activity against two human lung cancer cell lines, MOR-P (adenocarcinoma) and COR-L23 (large cell carcinoma) by using the SRB assay. Notable cytotoxic activity was shown by the bisindoles on together cell lines. This advises that, in assessment with the consistent monomeric indoles, at least part of together the ring systems present in the bisindoles is needed for cytotoxic activity. The strong alkaloids were additionally verified in contradiction of a human normal cell line (breast fibroblasts) and other human cancer cell lines together with StMI1 1a (melanoma), Caki-2 (renal cell carcinoma), MCF7 (breast adenocarcinoma), and LS174T (colon adenocarcinoma). The bisindoles O-acetylmacralstonine, villalstonine, and macrocarpamine were found to possess pronounced activity in contradiction of cancer cell lines with IC_{50} values in the range of 2–10 microM, by no discernible cell-type selectivity. Though, O-acetylmacralstonine showed obviously less toxicity contrary to normal breast fibroblasts (Keawpradub et al., 1999a).

9.3.4 SPERM MOTILITY-INHIBITING ACTIVITY

The methanol extract and the n-butanol fractions of the methanolic extract of *A. macrophylla* leaf were studied on the forward motility of mammalian spermatozoa. The results discovered that fraction-B (ursolic acid), a pentacyclic triterpene, has the possibility of sperm motility inhibition and can assist as a topical vaginal contraceptive (Chattopadhyay et al., 2005d).

The role of methanol solvent extract and n-butanol fraction of *A. macrophylla* leaf was inspected on the forward motility of goat spermatozoa. The methanol extract (600 µ/g/ml) and one n-butanol fraction (Fraction A; 100 µg/ml) showed considerable inhibition of sperm forward motility, verified by microscopic and spectrophotometric systems. About, 50–60% of the spermatozoa lost their motility after being treated with 600 µg/ml of methanol extract or 100 µg/ml of Fraction-A. The fraction-A at 400 µg/ml concentration discovered the entire inhibition of sperm forward motility at 0 min. The inhibitory activity enhanced the accumulative concentrations of the fraction. The motility inhibitory activity of the Fraction-A was constant to heat conduct at 100°C for 2 min. The compound displayed great inhibitory results in the pH range of 6.7–7.6. Fraction-A also designated great efficiency for inhibiting human sperm motility, assessed by the microscopic system. The Fraction-A (beta-sitosterol) is a powerful inhibitor of sperm motility, and therefore, it has the ability to act as a vaginal contraceptive (Chattopadhyay et al., 2005c).

9.3.5 ANTIPYRETIC ACTIVITY

The leaf extract showed a significant difference in fever by an albino rat as a model organism. Doses of 200 mg/kg caused a lowering of the body temperature up to 3 h following extract administration, as the normal temperature of 36.50°C at 0 h was reduced to 36.0°C at 3 h. While the maximum lowering of body temperature was noticed at 300 mg/kg of the leaf extract, as the mean temperature of 36.50°C was reduced to 35.40°C within a 3–5 h period in a dose-dependent manner (Arunachalam et al., 2005).

The *A. macrophylla* leaf methanol solvent extract and its fractions were confirmed on the normal temperature of the body and yeast-induced pyrexia in Wistar Albino rats. The leaf extract of oral doses at 200 and 300 mg/kg, and the n-butanol fractions of the extract at 50 mg/kg displayed a significant decrease in normal temperature of the body and yeast-provoked raised the temperature in a dose-dependent manner equal to that of normal antipyretic

drug paracetamol. The antipyretic consequence was ongoing at 1 hr. and prolonged for 5 hr. after the drug administration. The antipyretic result was more prominent when the fraction-A and fraction-B were administered together, showing that fraction-A and fraction B may contain antipyretic compounds which produce a preservative effect in combination (Chattopadhyay et al., 2005a).

9.3.6 VASORELAXANT ACTIVITY

Among isolated alkaloids of *A. macrophylla* vincamedine presented effective vasorelaxant activity, which may be arbitrated by inhibition of Ca^{2+} influx through voltage-dependent Ca^{2+} channels (VDCs) and/or receptor-operated Ca^{2+} channels (ROCs) as soon as partially mediated the NO release from endothelial cells. The occurrence of substituents together N-1 and C-17 may be significant to display vasorelaxation activity (Arai, 2012).

9.3.7 ANTIPROTOZOAL ACTIVITY

Methanolic and aqueous plant extracts were used to study antiprotozoal activity from 43 plant species. Among them, *Alstonia macrophylla* showed antiprotozoal activity at IC_{50} values below 10 μg/ml against *Trypanosoma brucei* (Camacho, 2003).

9.3.8 ANTIPLASMODIAL ACTIVITY

Among 13 alkaloids isolated by Keawpradub et al. (1999b), bisindole alkaloids from the methanolic extract of *A. macrophylla* leaves, stem bark, and root bark and evaluated the antiplasmodial activity in contradiction of the K1 strain of *P. falciparum* by used chloroquine diphosphate as a positive control and they showed significant activity.

9.3.9 NEUROLEPTIC ACTIVITY

Chatterjee and Dey (1964) estimated the neuroleptic activity of *A. macrophylla* by scheming the brain serotonin level in mice. Intraperitoneal administration of 116 (20 mg/kg) has revealed a result in the central nervous

system (CNS). Brain serotonin content was identified as 0.64 and 1.64 µg/g after 15, and 30 min of villalstonine administration.

9.3.10 ANTI-INFLAMMATORY ACTIVITY

Methanolic extract of dried leaves of *A. macrophylla* and its fractions were studied for its anti-inflammatory activity. The leaves extract at 200 mg kg^{-1} and 400 mg kg^{-1}, p.o. and its fractions at 25 mg kg^{-1} and 50 mg kg^{-1}, p.o. displayed significant dose-dependent anti-inflammatory activity in dextran-induced rats' hind paw edema (acute models) and carrageenan as well as in cotton pellet-induced granuloma (chronic model) in rats. The anti-inflammatory activity of the verified extract and its fractions were comparable with that of the standard drug indomethacin (10 mg kg^{-1}) (Arunachalam et al., 2002).

9.3.11 ANTIOXIDANT ACTIVITY

A. macrophylla extracts were found to be active free radical scavengers given that the IC_{50} value was very low at 0.71 mg/mL. The methanolic fraction of *A. macrophylla* leaves, precisely β-sitosterol, β-sitosteryl-β-D-glucoside, and ursolic acid, as well as a little amount of fraction, initiate to have alkaloid and fatty acids were the units that induced antioxidant activity at an in effect at 200 mg/kg (superoxide anion quenching experiments, DPPH protocol evaluations, and DNA cleavage assay) (Tan et al., 2019).

KEYWORDS

- **alkaloids**
- ***Alstonia macrophylla***
- **anti-inflammatory activity**
- **butyrylcholinesterase**
- **minimum inhibitory concentration**
- **phytochemistry**

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CHAPTER 10

Bioactives and Pharmacology of *Agave sisalana* Perrine

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10.1 INTRODUCTION

Sisal, *Agave sisalana* is an herbaceous monocotyledonous plant from the family Agavaceae. Sisal is mainly cultivated in semi-arid and tropical areas across the world (Oliveira and Helena, 2016). Sisal fibers isolated from the leaves of the plant are generally hard fibrous materials that are used in marine and agriculture industries (Zwane et al., 2010). As per FAO (Food and Agriculture Organization), the annual sisal production was around 3,20,000 Mg

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in the year 1998–2018. The edible part of sisal are leaves, stalks, sap, root, flowers, and basal rosettes (Vuorinne et al., 2021).

Only 3–5% of the leaf's decortication produces hard fibers which can be used for several purposes. Near about 95% is solid waste (mucilage) and liquid waste (juice) is generally discarded. The remaining waste is utilized either to feed animals or applied to crops for improving production. In most cases, these wastes are untreated and disposed of either burnt or dumped in the water. This approach is not practical and can lead to environmental pollution (Santos et al., 2009). Sisal waste primarily consists of water, plant tissue (cellulose and lignin), inorganic compounds, fibers, primary, and secondary metabolites (Viel et al., 2017). The waste can be used as fertilizers and shows great insecticidal properties against mosquito larvae which generally cause tropical diseases (Ade-Ajayi et al., 2011). Succinic acid isolated from sisal waste shows ovicidal activity against the nematodes of goats (Santos et al., 2017). Several types of research have been carried out to examine the chemical composition of sisal fibers in pulping and bleaching processes. The lipophilic extracts from *Agave sisalana* are utilized for the high-quality production of pulp and paper (Marques et al., 2010).

Sisal is a xerophytic, semi-perennial short plant that looks like a pineapple with a height of 1–2 m. Leaves are 10 cm wide, crescent, or sword-shaped covered by a waxy layer. Roots are 2–4 mm in diameter and spread horizontally up to 5 m. In general sisal plant produces 200–250 leaves in a span of 10–12 years (Onakpoma et al., 2020; Tewari et al., 2014). Sisal is a well-adapted plant to survive in dry and hot conditions. It can resist temperatures up to 50°C as well as can grow smoothly in 60–125 cm rainfall, along with that it survives drastic drought conditions (Naik et al., 2016). These plants can also survive lower temperatures in extremely cold winters. The life span of this plant is 8–10 years. Sisal fibers contain 66–72% of cellulose, 10–14% of lignin, and 12% of hemicellulose which makes it an outstanding material for manufacturing textiles, composites, etc. (Nayak et al., 2011). *A. sisalana* produces crude juice by leaves milling through acid hydrolysis. This crude juice is rich in saponins which are helpful for originating steroidal material known as sapogenins (more precisely hecogenin and tigogenin) (Dunder et al., 2013). Saponins are largely distributed in the plant kingdom, chemically they are also referred to as steroidal glycosides (Ribeiro et al., 2013). The saponin molecule consists of an aglycone non-sugar portion, i.e., sapogenins used for the semi-synthesis of several medicinal steroids such as corticosteroids, steroid diuretics, and sexual hormones (Cerqueira et al., 2012). Hecogenin is the steroidal saponin present in the leaves of *Agave* species.

After Hecogenin the other abundant steroidal saponin is tigogenin (Santos and Branco, 2014). Various saponins isolated from the plant source possess important physicochemical properties, i.e., emulsification, sweetness, bitterness, and solubility along with biological properties such as antimicrobial, insecticidal, and hemolytic (Ribeiro et al., 2013). These properties have applications in the cosmetics, pharmaceutical, and food industries. In addition, steroidal saponins present in sisal waste have immense applications in bioinsecticides as well as in the pharmaceutical industry (Figure 10.1) (Marques et al., 2010).

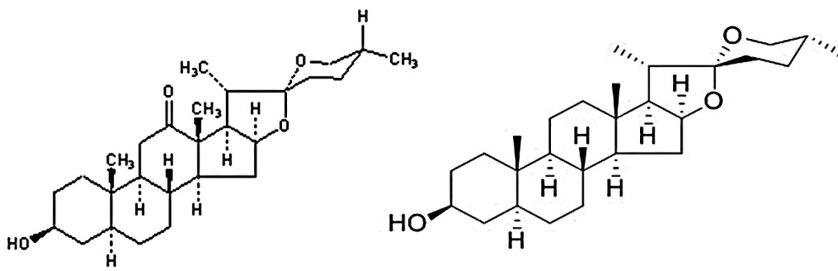


FIGURE 10.1 Structures of (a) hecogenin and (b) tigogenin.

Pre-Columbian farmers use *Agave* species for preparing fibers, soaps, shampoo, fermented beverages, and medicine (Parker et al., 2007). The leaves of sisal can grow up to five feet which can be used for making twine, nets, baskets, blankets, sandals, jewelry, fish stringers, dart boards, etc. (Debnath et al., 2010). In Chinese traditional medicines, saponins and polyphenols are the most important ingredient for biological effects (Ribeiro et al., 2013). Sisal is used for both industrial as well as domestic purposes, and also it has immense importance as a potent pharmaceutical drug. Various studies suggest the biological effect of *A. sisalana* as an anti-inflammatory, anti-microbial, and anthelmintic agent (Botura et al., 2013). *A. sisalana* liquid waste shows anthelmintic properties against GINs of small ruminants. This particular activity is generally seen due to the presence of secondary metabolites like alkaloids, saponins, and tannins (Botura et al., 2011). Agave syrups which are considered substitutes for sugar are also gaining popularity because of their antioxidant and antibacterial properties (Mellado-Mojica and Lopez, 2015). The methanolic extracts of sisal show promising effects against SF-268 and MCF-7 cancer cells (Chen et al., 2011). In addition to that flavones and homo-isoflavonoids were extracted from the methanolic extract of sisal leaves which inhibits the IL-2 and IFN-Y production in PBMC

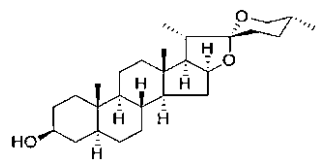
(peripheral blood mononuclear cells), resulting in immunopharmacological activity (Chen et al., 2009). *Agave* genus comprises more than 166 species, indigenous to semi-arid regions of Mexico. Most of the *Agave* species are of great commercial importance, for example, *Agave tequilana* also known as blue agave is used for preparing alcoholic beverages (Sarwar et al., 2019). *Agave* species consists of 20% non-structural carbohydrates which are used for the production of sweet drinks, distilled mescal, etc. (Santos et al., 2015).

The largest producer and exporter of sisal fiber worldwide is Brazil (Santos et al., 2017). *Agave* was introduced to various parts of the world and cultivated in Brazil, the West Indies, Indonesia, Africa, and other (Debnath et al., 2010). At present, Brazil is the major sisal fibers producing country, followed by Mexico, Tanzania, Kenya, and China (Naik, 2016). Agave plants are commonly found in Southwest America, Mexico, tropical, and south America along with parts of India (Hackman et al., 2006). The species of *Agave* are native to subtropical and tropical south and north America.

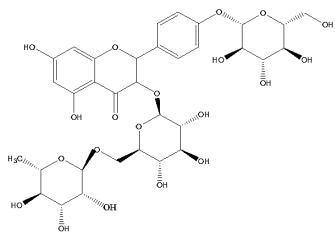
10.2 BIOACTIVES

A. sisalana contains saponins, and its roots are the best source of saponins. Hecogenin, 9(11)-dehydrohecogenin and tigogenin are the three major sapogenings. Hecogenin and tigogenin were isolated by Cripps and Blunden from the leaf and juice samples of *A. sisalana*. Hecogenin was found to show a gastroprotective effect in a study (Cerqueira et al., 2012). In 1993, three new steroidal saponins viz., dongnosides C, D, and E were isolated from the dried fermented residues of leaf juices of the plant. Later two major components, dongnosides A and B were also reported.

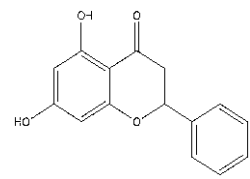
Three flavones (5,7-dihydroxyflavanone; Kaempferol 3-rutinoside-4-glucoside and Kaempferol 3-(2G rhamnosylrutinoside) and seven homoisoflavonoids (7-O-methyleucomol; 3-deoxysappanone; (±)-3,9-dihydroeucomin; dihydro-bonducellin; 7-hydroxyl-3-(4-hydroxybenzyl) chromane; 5,7-dihydroxy-3-(4-hydroxyl-benzyl)-4-Chromanone and 5,7-dihydroxy-3-(3-hydroxy-4-methoxybenzyl)-4-chromanone) were isolated from methanolic extract of the leaves of *A sisalana* (Debnath et al., 2010). These flavones and homoisoflavonoids were found to show immunopharmacological activity in a study and the structures of these compounds were elucidated based on spectroscopic analysis (Chen et al., 2009; Gutiérrez et al., 2008).



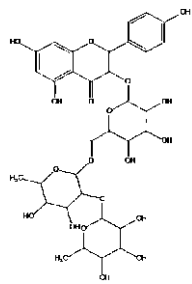
[3-hydroxyl-(25 R)-5-beta-spirostan-12-one]



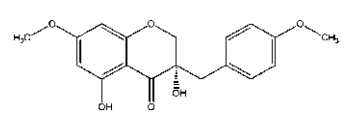
Kaempferol 3-rutinoside-4-glucoside



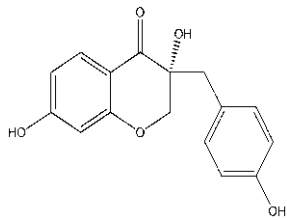
5,7-dihydroxyflavanone



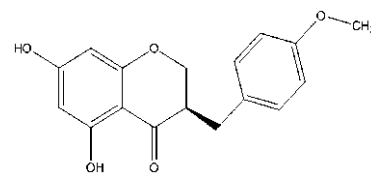
Kaempferol 3-(2G rhamnosylrutinoside)



homoisoflavonoids (7-O-methyleucomol



3-deoxysappanone



(±)-3,9-dihydroeucomin

10.3 PHARMACOLOGY

A. sisalana is useful in reducing blood pressure. *A. sisalana* possesses good antiseptic activities and stops the growth of bacteria in the stomach and intestine. *A. sisalana* is used in the treatment of syphilis. In pregnant animals *A. sisalana* stimulates the intestinal and uterine muscles, reduces

blood pressure, and can produce abortion. Traditionally the juice obtained from *A. sisalana* leaves has been used for the treatment of skin diseases in Northern Morocco (El-Hilaly et al., 2003). *A. sisalana* finds use in jaundice, other types of liver diseases, and tuberculosis. It acts as an emmenagogue and laxative (Debnath et al., 2010). *A. sisalana* is useful in constipation, indigestion, flatulence, and dysentery. Another use of *A. sisalana* is that its fibers soaked in water for a day can be used as a disinfectant for the scalp and a tonic for falling hairs. The gum obtained from the leaf and roots of *A. sisalana* is useful in the treatment of toothache. Diaphoretic and diuretic activities have been shown by the root of *A. sisalana*. Some specific pharmacological properties of *A. sisalana* are as in the subsections.

10.3.1 ANTHELMINTIC ACTIVITY

In a study, the anthelmintic activity of *A. sisalana* was studied in goats. The results of the study showed that *A. sisalana* produced a decrease in the larval count of the genus *Haemonchus* spp. *in vitro.* Also, in the *in vivo* test, there was a decrease in the *Oesophagostomum*, *Trichostrongylus*, and *Haemonchus* larva in goats that were in the fourth and fifth stages. In the above study, the activity of *A. sisalana* was shown to be better *in vitro* than *in vivo* (Domingues et al., 2010; Silviera et al., 2009; Tewari et al., 2014).

10.3.2 ANTIMICROBIAL ACTIVITY

A. sisalana has shown antimicrobial activity in various studies. It was found to be effective against various gram-negative bacteria, gram-positive bacteria, and fungi. Researchers have found it to be effective against *Escherichia coli, Streptococcus pyogenes, Candida albicans, Staphylococcus aureus, Salmonella typhi, B. cereus, M. luteus, S. cholereasuis, C. albicans, Shigella dysenteriae, Bacillus atrophaeus, Enterococcus faecalis, Pseudomonas aeruginosa, Bacillus stearothermophilus,* etc. (Ade-Ajayi et al., 2011; Tewari et al., 2014; Zwane et al., 2010; Hammuel et al., 2011).

10.3.3 ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES

Researchers have analyzed the analgesic and anti-inflammatory potential of *A. sisalana* by administering hexanic fraction obtained from *A. sisalana*

crude juice to animals. Different animal models were used to study the anti-inflammatory and analgesic potential of *A. sisalana*. The results of the study confirmed the anti-inflammatory and analgesic activity of *A. sisalana* (Tewari et al., 2014).

10.3.4 IMMUNOMODULATORY ACTIVITY

Flavonoids isolated from methanolic extract of leaves of *Agave sisalana* like (+/–)-3,9-dihydroeucomine, dihydrobonducellin, and 5,7,-dihydroxy-3-(4'-hydroxybenzyl)-4-chromanone demonstrated inhibitory action on the proliferation of PBMC, activated by phytohemagglutinin (PHA). The generation of interleukin-2 (IL-2) and interferon-gamma (IFN-γ) in activated PBMC were inhibited by the above-mentioned flavonoids in a concentration-dependent manner (Chen et al., 2009; Tewari et al., 2014).

10.3.5 GASTROPROTECTIVE ACTIVITY

Gastroprotective effects of hecogenin (a steroid saponin) isolated from *Agave sisalana* were demonstrated in a study. Indomethacin and ethanol-induced gastric ulcer models were used in the study. The results of the study indicated the gastroprotective and antiulcer potential of *A. sisalana* (Cerqueira et al., 2012).

10.4 CONCLUSION

A. sisalana is not only useful for obtaining fibers, but it can be useful in treating several diseases. Traditionally this plant has been used throughout the world for curing several ailments; thus, the medicinal potential of this plant is vast if explored properly. *A. sisalana* contains several important phytochemicals that possess important therapeutic activities. *A. sisalana* can be studied in detail for these phytochemicals so that new formulations useful in a variety of diseases can be developed. *A. sisalana* has tremendous potential for becoming an important medicinal plant for numerous health conditions in humans if it is investigated thoroughly.

KEYWORDS

- ***Bacillus atrophaeus***
- **flavonoids**
- **gastroprotective activity**
- **interferon gamma**
- **interleukin-2**
- **peripheral blood mononuclear cells**
- **phytohemagglutinin**
- ***Shigella dysenteriae***

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CHAPTER 11

A Review on Phytochemistry and Biological Activities of *Aerva javanica* (Burm. f.) Juss. ex Schult.

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11.1 INTRODUCTION

Since ancient times, nature has been a large reservoir of cures in the form of medicinal herbs for the treatment of a variety of maladies. The therapeutic properties of the plants in the genus *Aerva* (family Amaranthaceae) are well-known. In numerous parts of the world, the common folk has traditionally used them for their medical virtues. This demonstrates the extraordinary herbs' potency (Musaddiq et al., 2018). Among the many medicinal herbs offered by nature, *Aerva javanica* (Burm. f.) Juss. ex Schult. is one such blessing. It is a perennial, erect to scandent dioecious

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conspicuous undershrub, 0.6–1 m tall, found in temperate Africa and Asia and widely seen in many countries (Judd et al., 2008). In both traditional and modern medical systems, it has been widely used for a variety of ailments (Deshmukh et al., 2008). It is branched at the base with the branches being pubescent or woolly-tomentose. Leaves are simple, alternate, and sessile, with lamina being linear-oblong or oblong-spathulate, along with obtuse or acute apex and tapering base, and have white cottony hairs underneath. The dioecious flowers occur in the form of clusters on sessile and cylindrical spikes. Male and female flowers are different, e.g., outer petals range from 1.5–2.25 mm in male flowers while in female flowers size of two outer petals ranges from 2–3 mm, and three inner petals are slightly shorter. In male flowers filaments are delicate, and anthers are almost equal to the perianth, while female flowers lack anthers and reduced filaments are present. The female plant bears a small ovary with a short style. Stigma is a rudimentary and compressed round capsule with a size of 1–1.5 mm present. Black and brown colored round or slightly compressed seeds are present which range in size from 0.9–1.25 mm. It is commonly known as kapok bush or desert cotton or pillow weed or snow bush in English and belongs to the Pashanbheda group of plants which, according to Ayurveda, is used to dissolve the stones in the urinary tract. It has synonyms *Aerva tomentosa* Forssk., *Achyranthes javanica* Pers., *Aerva persica* (Burm. f.) Merr., *Aerva wallichii* Moq., *Celosia lanata* L., *Iresine javanica* Burm. f. and *Iresine persica* Burm. f.

11.2 PHYTOCHEMICAL CONSTITUENTS

Flavonoids, phenolic acids, coumarins, tannins, glycosides, cardiac glycosides, resins, diterpenes, triterpenes, sterols, saponins, alkaloids, anthraquinones, and carbohydrates were found in the phytochemical screening of *A. javanica* extracts from various parts (Srinivas and Reddy, 2012; Abbas et al., 2014; Nawaz et al., 2015; Karthishwaran et al., 2018; Suleiman, 2019). When compared to the other extracts, the methanol extract had the most phytochemicals (Anand et al., 2014; Karthishwaran et al., 2018). Furthermore, root extract included a high concentration of alkaloids and saponins, but aerial parts extract contained a high concentration of triterpenes and flavonoids (Suleiman, 2019). *In vitro* leaf extract has the highest levels of flavonoid and phenolic compounds, followed by callus extract and wild leaf extract (Selvakumar and Kamalanathan, 2019).

11.2.1 PHENOLIC COMPOUNDS

Polyphenolic compounds are abundant in *A. javanica*. Ethyl acetate (EA) fraction of flowers has been reported to contain a number of flavonoids and/or their glycosides, e.g., kaempferol-3-O-β-D-[4‴-E-p-coumaroyl-α-Lrhamnosyl-(1→6)]-galactoside, kaempferol-3-O-β-D-[4‴-E-pcoumaroyl-α-L-rhamnosyl-(1→6)]-(3″-E-p-coumaroyl) galactoside, kaempferol-3-O-β-D-[4‴-E-p-coumaroyl-α-L-rhamnosyl-(1→6)]-(4″-E-p-coumaroyl) galactoside, kaempferol-3-O-(4″,6″-di-O-E-p-coumaroyl)-β-D-glucopyranoside, isorhamnetin-3-O-β-D-(6-p-coumaroyl) glucopyranoside and isorhamnetin-3-O-(4″,6″-di-O-E-p-coumaroyl)-β-D-glucopyranoside along with other phenolics, i.e., gallic acid, caffeic acid, p-coumaric acid, hexadecyl ferulate, hexacosyl ferulate and eicosanyl trans-p-coumarate (Mussadiq et al., 2013). Kaempferol-3-galactoside, 3-rhamnogalactoside, quercetin-3-galactoside, isorhamnetin-3-galactoside, 3-rhamnosyl-(1→6)-galactoside and 3-(p-coumaroyl)-rhamnogalactoside, Chrysin-7-O-galactoside have been isolated from the fresh aerial parts of *A. javanica* (Garg et al., 1979, 1980). A new flavonol, isorhamnetin 3-O-β-[4‴-p-coumaroyl-α-rhamnosyl(1→6) galactoside], has been isolated from *A. javanica* along with its unacylated derivative, its kaempferol analog, and various common kaempferol, quercetin, and isorhamnetin glycosides (Saleh et al., 1990). From the perianth lobes of this plant a rare acylated flavonol glycoside kaempferide-3-O-(6″-O-acetyl-4″-O-α-methylsinapyl)-neohesperidoside has been isolated (Jaswant et al., 2003). Alcoholic extract of roots of *A. javanica* contains 0.02196% wt./wt. quercetin (Movaliya and Zaveri, 2012). Methanolic extracts of leaf and flower of *A. javanica* were evaluated by HPTLC analysis to identify the important phenolic compounds such as apigenin, quercetin, azalea tin, kaempferol tricin and chlorogenic acid (Srinivas and Reddy, 2012). Rutin (3,3,4,5,7-pentahydroxyflavone-3-rhamnoglucoside), a biflavonoid was reported in aerial parts of *A. javanica* ethanolic extracts (Ahmed et al., 2016). Other flavonoids isolated from *A. javanica* whole plant extract are apigenin-7-O-glucuronide, isoquercetrin, 5-methylmellein (Sharif et al., 2011), and Chrysoeriol, isorhamnetin 3-0-rutinoside, kaempferol 3-0-robinoside (Radwan et al., 1999).

11.2.2 TERPENOIDS

Four new ecdysteroids (Aervecdysone A-D), along with three known steroids, 24-epi-makisterone A, deoxyintegristerone A, and β-ecdysone were isolated from the methanolic extract of the flowers of *A. javanica*. All isolates

were evaluated for their inhibitory activities against the enzymes acetylcholinesterase (AChE), butyryl-cholinesterase, and lipoxygenase (Saleem et al., 2013). The sterols reported in *A. javanica* were campesterol, 7-ergosterol, spinasterol, 7-stigmastenol, campestenol, sitosterol, and 22-stigmasterol (Patterson et al., 1991). Lupeol, β-amyrin, β-sitosterol, and betulinic acid, were isolated from the *A. javanica* (El-Seedi et al., 1999). The EA extract of the fresh leaves of *A. javanica* yielded compounds such as β-sitosterol glucoside and oleanolic acid (Usmanghani et al., 1982). β-Sitosterol, α- and β-amyrin, and pentadecanoic acid have been reported in GLC analysis of unsaponifiable fractions of *A. javanica* (Radwan et al., 1999). Ursolic acid, a pentacyclic triterpenic acid was isolated from whole plant hydro methanolic extract of *A. javanica* (Khan et al., 2012).

11.2.3 ALKALOIDS

Ammar et al. (1996) isolated two important alkaloid compounds, namely, 10-methoxy-canthin-6-one (Methyl aervin) and 10-hydroxy-canthin-6-one (aervin). The presence of allantois and indole acetic acid was reported in the methanolic extract of flowers of *A. javanica* (Musadiq et al., 2017).

11.2.4 OTHER SECONDARY METABOLITES

The essential oil of *A. javanica* leaves was found to be rich in hentriacontane (21.48%), nonacosane (20.59%), heptacosane (19.78%), pentacosane (5.58%), octacosane (3.47%), triacontane (2.81%) and hexacosane (2.04%), whereas the essential oil of stems was determined to be rich in nonacosane (23.26%), heptacosane (22.48%), hentriacontane (18.32%), octacosane (3.42%), triacontane (2.24%) and squalene (2.07%) (Samejo et al., 2012). Samejo et al. (2013) also reported that the essential oils (EOs) obtained by hydrodistillation from seeds were heptacosane (25.4%), 3-allyl-6-methoxyphenol (14.1%), pentacosane (12.1%), 6,10,14-trimethyl-2-pentadecanone (7.9%), nonacosane (7.1%), tricosane (3.6%), α-farnesene (3.5%), dodecanal (2.7%) and octacosane (2.1%) and by steam distillation (SD) from seeds were heptacosane (41.4%), pentacosane (21.2%), nonacosane (14.8%), tricosane (6.3%), octacosane (4.2%) and tetracosane (3.0%). Khan et al. (2012) revealed two phytoconstituents, 3-hydroxy-4 methoxybenzaldehyde, and (E)-N-(4-hydroxy-3-methoxyphenethyl)-3-(4-hydroxy-3-ethoxyphenyl) acryl amide. Gas chromatography-mass spectrometry (GC-MS) analysis of

the n-hexane, EA, and methanol extracts revealed the presence of various bioactive compounds. Indole was found to be a major component followed by Sulfallate (2-Chlorallyl diethyldithiocarbamate (CDEC), Carbaril, Bis(2-ethylhexyl) phthalate, Quinoline, 4H-Cyclopenta[def]phenanthrene,2-[Bis(2-chloroethylamino)]-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide, phenobarbital, 1H-Indole, 2-methyl-, 2,3,7,8-Tetrachlorodibenzo-p-dioxin Disulfide, diphenyl (Karthishwaran et al., 2018).

Nutrient evaluation of *A. javanica* showed round about 70% carbohydrate, 7.3% moisture, 1.1% fats, 319.5 Kcal/100 g of energy, and 29.1% fiber content. Elemental analysis of *A. javanica* has shown the presence of different elements. Some of them are Cu (2.13 ppm), Mn (0.64 ppm), Pb (0.38 ppm), Cd (0.06 ppm), Fe (2.77 ppm), Cr (3.65 ppm), Mg (29.93 ppm), Na (28.46 ppm) (Figure 11.1) (Hussain et al., 2011).

11.3 PHARMACOLOGICAL ACTIVITIES

A. javanica has various applications in folk medicine. Extracts from these plants are of great importance because of their ethnopharmacological properties.

11.3.1 ANTIMICROBIAL ACTIVITY

Extracts (hexane, chloroform, and methanol) of various parts of *A. javanica*, including flower, leaves, roots, and stem, were evaluated against bacteria (*Escherichia coli*, *Enterobacter aerogenes*, *Klebsiella penumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Salmonella typhimurium*, *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*) showed that methanolic extracts of flower and leaves had more potent antibacterial activity. Methanolic extracts of flower and leaf extracts were shown to have more significant antibacterial activity. In addition, the methanolic extract included a considerable number of phytochemicals, indicating a broad range of antibacterial action. The zone of inhibitions for a methanolic extract of leaves and flowers against the test bacteria were found to be 16 to 12 mm and 16 to 9 mm, respectively (Srinivas and Reddy, 2012). Significant microbial activities were reported against *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella typhi*, *Trichophyton longifusus*, *Shigella flexneri*, *Escherichia coli*, *Candida albicans*, *Pseudomonas aeruginosa*, *Candida glabrata*, *Microsporum canis*, and

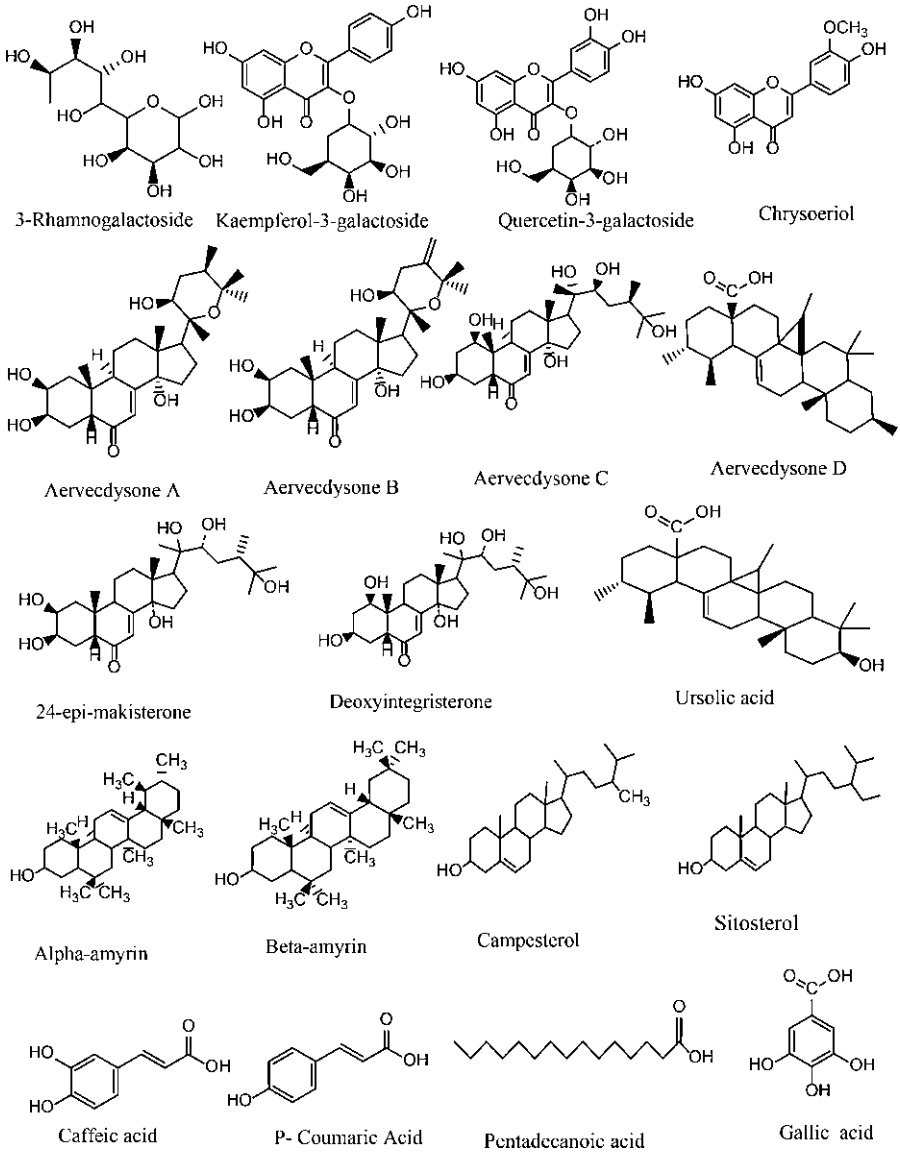


FIGURE 11.1 Phytochemical constituents isolated from *Aerva javanica*.

Fusarium solani by flavonoids isolated from extracts of *A. javanica* (Sharif et al., 2011). The flavonoidal constituents (isorhamnetin 3-0-rutinoside and chrysoeriol) isolated from EA fraction of aqueous and alcoholic extracts of *A. javanica* showed significant antimicrobial activity against gram-negative

bacteria, yeast, and fungi (Radwan et al., 1999). The fraction of secondary metabolites possesses strong antibacterial activity against the selected human pathogens viz., *Staphylococcus aureus* and *Proteus vulgaris* (Selvakumar and Kamalanathan, 2019). Antimicrobial activities have been reported for dichloromethane, ethanol, and methanol extracts of *A. javanica* (Al-Fatimi et al., 2007). The perianth lobes of *A. tomentosa* showed antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* (Jaswant et al., 2003). Another report revealed that the extract of *A. javanica* inhibited the growth of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus aureus* except *Salmonella typhi* (Mufti et al., 2012). Reddy and Reddy (2009) have reported the antimicrobial activity of leaves of *A. javanica* extracted with petroleum ether (PE), EA, and methanol. The crude methanolic leaf extracts showed significant antibacterial and antifungal activity. However, hexane extracts did not show any activity. The disc diffusion method performed for antimicrobial activity revealed weak activities in *A. javanica* root extracts (100 µg/ml) against Gram-positive bacteria (*Candida albicans* and *Staphylococcus aureus*) and Gram-negative (*Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Shigella flexneri*). However, the aerial parts extract showed no activity against the pathogens tested (Suleiman, 2019). Extracts of *A. javanica* were tested for antifungal activity against *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, and *Fusarium solani*, but poor activity was observed (Mufti et al., 2012). Khader et al. (2012) evaluated the antifungal activity of butanol, methanol, ethyleactate, chloroform, *n*-hexane, and water crude fraction of *Aerva javanica*. The *n*-hexane crude fraction of *Aerva javanica* was found active against all three tested fungal strains *Fusarium nigar, Aspergillus fumigatus,* and *Aspergillus solani.* The highest zone of inhibition resulting from *n*-hexane crude fraction was 11 mm against *Aspergillus fumigatus.* Butanol crude fraction showed a 12 mm zone of inhibition against *Fusarium nigar*.

11.3.2 ANTIOXIDANT ACTIVITY

The radical scavenging effect of the *A. javanica* aerial parts extract, which had a greater quantity of total phenolic compounds (228.02 mg GAE/100 g) and total flavonoid content (99.24 mg QE/100 g) was also determined to be stronger in both 1,1-diphenyl-2-picrylhydrazyl (DPPH) (IC_{50} = 28.54 µg/mL) and H_2O_2 (IC_{50} = 154.17 µg/mL) assays compared with the standard

antioxidant ascorbic acid (DPPH: IC_{50} = 27.27 µg/mL; H_2O_2: IC_{50} = 164.90 µg/mL) (Suleiman, 2019). The methanolic extract of the leaves of *A. javanica* was evaluated for its total antioxidant capacity by hydroxyl radical scavenging activity, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging, superoxide radical scavenging activity, and ABTS radical scavenging activity assays and its total phenolic content was also determined and the results were found to be related to each other (Karthishwaran et al., 2018). Murtaza et al. (2014) reported that the methanolic extract of *A. javanica* shows comparatively high antiradical activity than the acetone extract. The highest IC_{50} value for scavenging activity of *A. javanica* was shown by 80% methanol extract (46.5 ± 2.2 µg/ml) followed by chloroform extract (78.3 ± 3.6 µg/ml). On the other hand, the extract prepared in n-hexane showed no scavenging activity effect (IC_{50} > 1,000 µg/ml) (Eltayeb et al., 2017). Antioxidant studies prove to show potent antioxidant activity for hexane, chloroform, acetone, and aqueous extracts of aerial parts of *Aerva tomentosa* (Yogananda et al., 2011). In another study, this plant was subjected to evaluate its methanolic, ethylacetate, DCM, and aqueous extracts for their antioxidant potential and total phenolic components. In the DPPH scavenging assay, the RC_{50} value of the methanol extract was found to be 6.0 µg/ml. The highest amount of total phenolic contents found in the methanol soluble fraction was 0.726 mg/g extract. As a result, it was found that methanolic extract was rich in total phenolics and was a more potent antioxidant than other extracts thus showing the structure-activity relationship between phenolics and antioxidant activity (Sethi and Sharma, 2011). Alcoholic and aqueous extracts of *A. javanica* root have been found to show potent scavenging abilities against free radicals, reducing abilities for iron and inhibitory properties against lipid peroxidation (LPO) (Movaliya and Zaveria, 2014a). Water extract of *A. javanica* leaves and stem was found to be comparatively rich in phytochemicals and antioxidant properties when compared with methanol and hexane extracts, which suggests the preferable use of polar solvents for extraction of such substances from plant material (Nawaz et al., 2015). *In vitro* assays of *A. javanica* ethanolic extracts (31.25–500 µg/mL) revealed the strong free-radical scavenging ability of the extract and the presence of rutin, a well-known antioxidant flavonoid, was identified (Ahmed et al., 2016). The high phenolic (44.79 ± 3.12 mg GAE/g) and flavonoid (28.86 ± 0.12 mg QE/g) content of *A. javanica* corresponds to its strong antioxidant capacity in the ABTS, FRAP, and CUPRAC assays, with values of 101.41 ± 1.18, 124.10 ± 1.71, and 190.22 ± 5.70 mg TE/g, respectively (Saleem et al., 2021).

11.3.3 ANTIULCER ACTIVITY

Various fractions of *A. javanica* were tested for inhibition of urease enzymes for their potential against ulcers. EA fraction of methanolic extract exhibited moderate anti-ulcer activity with 50% inhibition at a concentration of 0.2 mg/mL as compared to other fractions. Bioactive compounds such as 3-hydroxy-4 methoxybenzaldehyde, ursolic acid, and (E)-N-(4-hydroxy-3-methoxyphenethyl)-3-(4-hydroxy-3-ethoxyphenyl) acryl amide was isolated from whole plant hydro methanolic extract, which were studied for an anti-urease activity where they showed 15.3, 33.4, and 64.6% of inhibition of the urease enzyme. (E)-N-(4-hydroxy-3-methoxyphenethyl)-3-(4-hydroxy-3-ethoxyphenyl) acryl amide showed marked anti-ulcer activity which might be due to the presence of amide group (Khan et al., 2012).

11.3.4 ANTIDIARRHEAL ACTIVITY

In Ayurveda, *A. javanica* is known as "Valleyaka" and the root is used as an antidiarrheal drug (Yoganarasimhan, 2000). A study was undertaken to evaluate the effect of vacuum-dried ethanolic and aqueous whole plant extracts of *A. javanica* at a dose of 800 mg/kg with reference standard as loperamide (5 mg/kg) for their antidiarrheal potential and action on small intestinal transit in albino rats. Ethanolic and aqueous extracts significantly inhibited castor-oil-induced diarrhea and the percentage of inhibition was 92 and 88, respectively. The extracts also reduced the intestinal transit in the charcoal meal test when compared with the control (1% carboxy methyl cellulose). The ethanolic plant extracts were more effective than aqueous plant extracts against castor-oil-induced diarrhea. The result obtained to establish the efficacy of these plant extracts as antidiarrheal agents (Joanofarc and Vamsadhara, 2003).

11.3.5 NEPHROPROTECTIVE ACTIVITY

The aqueous extract of *A. javanica* roots at a dose of 200 and 400 mg/kg was evaluated for its nephroprotective activity in male Wistar albino rats. It was observed that cisplatin injury was evidenced by the elevated biochemical markers (blood urea, serum creatinine, total protein, and serum albumin, urine volume, urine PH) and histopathological features of acute tubular necrosis. The aqueous extract at the dose level of 400 mg/kg body weight

was found to normalize the elevated biochemical markers and bring about a marked recovery in kidneys as evidenced microscopically (Movaliya et al., 2011). The alcoholic extract of the root of *A. javanica* possesses marked nephroprotective activity as compared to aqueous extract in biomarkers and LPO assay (Movaliya and Zaveri, 2014a). The hexane extract of *A. javanica* root has been also found to be effective against cisplatin-induced renal toxicity due to its nephroprotective activity (Movaliya and Zaveri, 2014b). The alcoholic extract of the root of *A. javanica* was shown to possess significant nephroprotective activity against cisplatin- and gentamycin-induced renal toxicity in experimental animals (Kumar et al., 2008).

11.3.6 HEPATOPROTECTIVE ACTIVITY

The hepatoprotective salutation of *A. javanica* ethanolic extracts in carbon tetrachloride (CCl_4)-intoxicated rats was evaluated by serum biochemistry and histopathology. Oral administration of the extract (100 and 200 mg/kg.bw/day) significantly normalized the serum glutamate oxaloacetate transaminase (GOT), serum glutamate pyruvate transaminase (GPT), gamma-glutamyl transferase, alkaline phosphatase (ALP), bilirubin, cholesterol, high-density lipoprotein, low-density lipoprotein, very-low-density lipoprotein, triglyceride, and malondialdehyde (MDA) levels, including tissue nonprotein sulfhydryl and total protein in CCl_4-injured rats. In addition, the histopathology of the dissected liver also revealed that *A. javanica* cured the tissue lesion compared to silymarin treatment. Ethanolic extracts of this plant further showed strong *in vitro* anti-oxidative and anti-lipid peroxidative activities, evidenced by the presence of alkaloids, flavonoids, tannins, sterols, and saponins. Identification of Rutin (2.53 μg/mg), a biflavonoid strongly supported hepatoprotective solution of extract (Ahmed et al., 2016). A rare acylated flavonol glycoside kaempferide-3-O-(6″-O-acetyl-4″-O-α-methylsinapyl)-neohesperidoside isolated from perianth lobes of *A. tomentosa* showed hepatoprotective activity against liver damage induced by CCl_4 in rats (Jaswant et al., 2003).

11.3.7 CYTOTOXIC AND ANTITUMOR ACTIVITY

The cytotoxic effect of the three extracts (chloroform, methanol, n-hexane) was assessed on two different breast cancer cell lines, MDA-MB-231 and MCF7, using (4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide

(MTT) assay. The three extracts exhibited variations in their cytotoxic effect on the two examined breast cancer cell lines with different IC_{50} values. The result showed that the chloroform extract exerted an inhibitory effect in a concentration-dependent manner on both cancer cell lines with IC_{50} values of 32.7 ± 0.7 µg/ml and 40.9 ± 2 µg/ml on MDA-MD=321 and MCF7, respectively. Around 80% methanol extract exhibited a cytotoxic effect on MCF7 with IC_{50} value of 96.6 ± 2.9 µg/ml, whereas had no cytotoxic effect on MDA-MB-231 cell line (IC_{50} > 200 µg/ml). n-hexane extract was found to be less cytotoxic against both cancer cell lines with IC_{50} values of 178.3 ± 3.7 and 196.9 ± 2.8 µg/ml on MDA-MB-231 and MCF7, respectively. Thus *A. javanica* shows a moderate cytotoxic effect on two different breast cancer cell lines with some cyto-selectivity towards MDA-MB-231 compared to MCF7 breast cancer cell line (Eltayeb et al., 2017).

11.3.8 ANTIDIABETIC ACTIVITY

The antidiabetic activity of ethanol extract of *A. javanica* leaves was studied at three doses (100, 200, and 400 mg/kg) in alloxan-induced diabetic mice. There was a significant dose-dependent decrease in blood glucose level and a maximum reduction in serum glucose level was observed (241.86 mg/dl) on the 35th day at the dose of 400 mg/kg on the 35th day. Further, 400 mg/kg dose significantly increased the glucose threshold in non-diabetic and diabetic mice at 60 min after administration of glucose (Srinivas and Reddy, 2009). In a comparative study, it was noticed that *A. lanata* polysaccharide has greater hypoglycemic activity as compared to that of *A. javanica*, which may be attributed to the difference in complexity of their structures (Aboutabl et al., 1998).

11.3.9 ANTI-INFLAMMATORY ACTIVITY

The anti-inflammatory effects of ethanolic crude extracts of *A. javanica* whole plant were investigated in carrageenan-induced paw edema in rats. Administration of ethanolic extract (250 mg/kg and 500 mg/kg) significantly reduced the edema thickness in a time and dose-dependent manner. The inhibition percentage of inflammation was 48.30% and 85.22% at a dose of 250 and 500 mg/kg at the 30th hour, respectively. The ethanolic extract at a dose of 500 mg/kg shows a potent activity to be nearly the same comparable

to inhibition produced by indomethacin (reference drug) at the last hour of following up (Elsaeed et al., 2015).

11.3.10 ANTIMALARIAL ACTIVITY

Stem, leaf, and mature fruit extracts of *A. javanica* (3, 2.70, 4 mg dry extract/80 mg dry plant material) of *A. javanica* kills *Plasmodium falciparum;* showed IC_{50} values of 308, 100, and 76 µmol/mL, respectively (Simonsen et al., 2001). *In vitro* experiments for antimalarial efficacy of *A. javanica* whole plant extract against *Plasmodium falciparum* schizonts maturation revealed a 100% inhibition of parasite growth at a dose of ≤500 µg/ml (Ahmed et al., 2010).

11.3.11 OTHER BIOLOGICAL ACTIVITIES

Aqueous extracts of this plant exhibited dose-dependent smooth muscle relaxant effects and significant antispasmodic activity (Wassel et al., 1997). A crude extract of *A. javanica* exhibited weaker acetylcholinestrase inhibitory activity with an IC_{50} value of 275.2 µg/mL (Murtaza et al., 2013). *A. javanica* also showed antiviral activity (Baltina et al., 2003). According to a study based on the analysis of LC-MS/MS and other biological activities, *A. javanica* can be used as functional food ingredients and as well as for pharmaceutical purposes in the treatment of many oxidation-based diseases such as aging, neural disorders, and genetic mutations such as cancer (Yasir et al., 2016).

KEYWORDS

- **acetylcholinestrase inhibitory activity**
- ***Aerva javanica***
- **antimalarial efficacy**
- **carbon tetrachloride**
- ***Celosia lanata***
- **gas chromatography-mass spectrometry**

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CHAPTER 12

Phytochemistry and Pharmacology of Prince's Feather Amaranth (*Amaranthus hypochondriacus* L.; Family: Amaranthaceae)

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12.1 INTRODUCTION

Amaranthus hypochondriacus L. is an ornamental herb cultivated worldwide and believed to originate from North America. The plant is commonly known as Prince's Feather Amaranth. The plant is used as a grain crop in Central America, South America, and Asia. The seed is popped, roasted, and powdered to make bread, and used as a grain. *Amaranthus hypochondriacus* is an annual herb growing up to 2 m with an erect and branched stem. The leaves are arranged spirally and have a long petiole, and the blade is broadly lanceolate to rhombic-ovate. The inflorescence is terminal, forming a branched cluster of cymes arranged axillary. The inflorescence is dark red, purple, or deep beet-red in color. The flower is unisexual with long bracteoles and small tepals 5 in number. The seeds are 1 mm long, obovoid to ellipsoid, and whitish, yellowish, blackish, or dark reddish-brown (Jansen et al., 2004).

The plant's young leaves are a rich source of vitamins and minerals; they are cooked and consumed like spinach. The roasted seeds are used to

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make popcorn, and the sprouted seeds, are used in salads. The red pigment obtained from the flowers finds its usage as a food coloring agent (Facciola, 1990). The plant has medicinal value and is used as an astringent lotion and applied on the skin to prevent bleeding due to minor injury. The plant extract can be taken internally to treat excessive bleeding due to menstruation and diarrhea. The leaves are dried, powdered, and used as herbal tea. The dried parts of the plant are mixed with warm water and used for gargling to cure throat infections, inflammation of the pharynx, and mouth ulcers. The plant finds its external use in treating nosebleeds and excessive vaginal discharge (Brown, 2003). The amaranth seed is rich in micronutrients, phytochemicals, and macronutrients such as protein, dietary fibers, carbohydrates, and lipids. The content of unsaturated fats such as linoleic fatty acid (25–62%) and 0.3–2.2% alpha-linolenic fatty acid (0.3–2.2%) is high in amaranth grain (Soriano-García and Aguirre-Díaz, 2019). Amaranth also contains numerous essential amino acids and essential oils (EOs). Amaranth is a rich source of lysine, which the organism itself cannot synthesize. Moreover, the amaranth grain is gluten-free; hence it can be consumed by patients with celiac disease. Amaranth grain flour can be used as a substitute for regular flour for preparing baked food. The amaranth seed's basic nutrition value and energy content were estimated in 100 grams of the grain *viz.*, Carbohydrates (65.25 g); Proteins (13.56 g); Lipids (7.02 g); Dietary fibers (6.70 g); Water (11.290 g); Energy (371 kcal); Calcium (159 mg); Magnesium (248 mg); Phosphorus (557 mg); Iron (7.61 mg); Potassium (508 mg); and Sodium (4 mg) (Raw, 2015).

12.2 BIOACTIVE COMPOUNDS

Studies revealed that amaranth is a good source of critical phytochemical constituents, including phenols, polyphenols, steroids, organic acids, and nitrogen-containing compounds. Reports indicate that the total phenol content of *A. hypochondriacus* grain was 0.8459 mg gallic acid equivalents (GAE)/100 mg extract, and the total flavonoid content was 0.629 mg Catechin Equivalent/100 mg extract. The total percentage of alkaloids and saponins content is around 5.57% and 0.06%, respectively. The alkaloid content of amaranth grain helps in healing wounds, skin burns, ulcers, and hemorrhoids. In contrast, the saponin content helps in improving nutrient absorption, the immune system, and control of blood cholesterol levels (Bhat et al., 2015). *A. hypochondriacus* grain contains betacyanin and betaxanthin. Further, reports indicate that among the phenolic compounds, gallic

acid, vanillic acid, ellagic acid, ferulic acid, sinapic acid, and p-coumaric acid are most abundant in *A. hypochondriacus* grain extract (Li et al., 2015). In contrast, isoquercetin, and rutin are the most abundant flavonoids reported in the grain extract (Khanam and Oba, 2013). De La Rosa et al. (2009) reported polyphenols such as nicotiflorin, quercitrin, syringic acid, 4-hydroxybenzoic acid, vanillic acid, rutin, and isoquercitrin in four different commercial varieties *A. hypochondriacus* grain flour. Agarwal et al. (2019) reported two new alkylated phenols: 3-(3,5-di-tertbutyl-4-hydroxyphenyl) propanoic acid 2,4-di-tert-butyl phenol in the n-hexane leaf extract of *A. hypochondriacus* by application of GC-MS metabolite profiling of hexane leaf extract. Further, the GC-MS Chromatography study of the hexane leaf extract of *A. hypochondriacus* indicates squalene, butanoic acid, phosphoric acid, nonadecene, myristic acid, eicosene, stearic acid, linolenic acid, hexacosanoic acid, octacosanoic acid, monopalmitin, cholesterol, α-tocopherol, triacontanol, and α-amyrin. β-carotene and vitamin C (ascorbic acid) are the two major bioactive compounds found in the fresh leaf extract of *A. hypochondriacus* (Sarker and Oba, 2020). Steroids such as campestrol, spinasterol, β-sitosterol and stigmasterol are abundant in *A. hypochondriacus.* Further studies revealed that *A. hypochondriacus* is rich in monounsaturated fatty acids, especially oleic acid, present in a high percentage (+39%). Other fatty acids such as linoleic acid and palmitic acid are present in the leaf extract of *A. hypochondriacus* (El-Gendy et al., 2018). *A. hypochondriacus* seed is rich in lunasin-like peptides and other potential bioactive peptides (Silva-Sánchez et al., 2008). Montoya-Rodríguez et al. (2015a) reported the presence of 11S globulin, prosystemin, 7S globulin, ring-zinc finger protein, and trypsin inhibitor as the principal essential protein in amaranth seed. The important bioactive compounds found in *A. hypochondriacus* are given in Figures 12.1–12.3.

12.3 PHARMACOLOGY

12.3.1 ANTIRADICAL ACTIVITY

The antioxidant property of the flower and leaf extract of *Amaranthus hypochondriacus* was studied via DPPH radical scavenging assay and the cyclic voltammetry method. The antiradical activity of flower and leaf extract was concentration-dependent. The antioxidant activity of amaranth flower extract was higher than the leaves extract, which indicates that amaranth flower

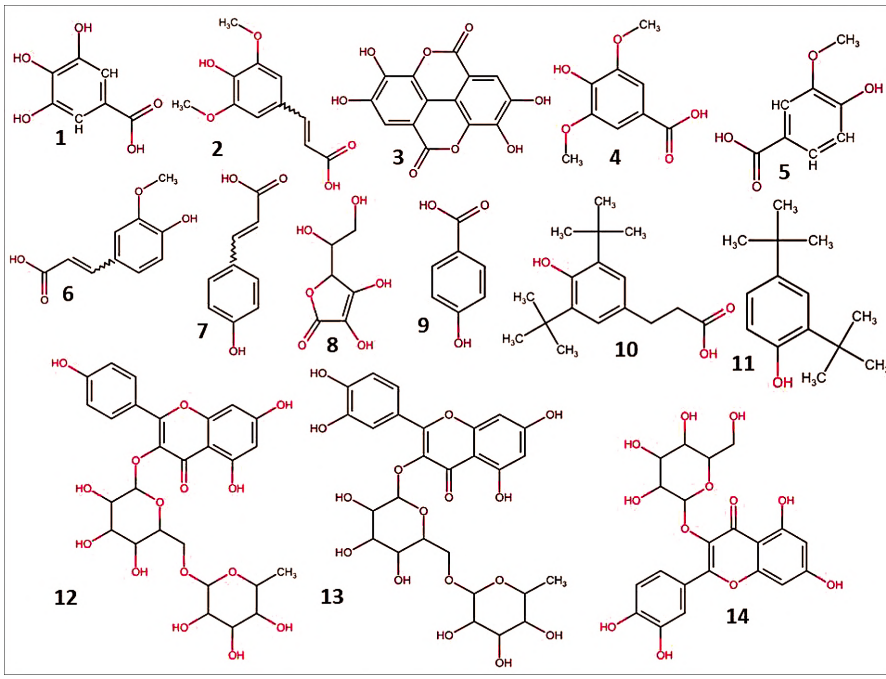


FIGURE 12.1 Important bioactive compounds (phenols, flavonoids, fatty acids, and steroids) found in *A. hypochondriacus* – (1) gallic acid; (2) sinapic acid; (3) ellagic acid; (4) syringic acid; (5) vanillic acid; (6) ferulic acid; (7) p-coumaric acid; (8) ascorbic acid; (9) 4-hydroxybenzoic acid; (10) 2,4-di-tert-butyl phenol; (11) 3-(3,5-di-tertbutyl-4-hydroxyphenyl) propanoic acid; (12) nicotiflorin; (13) rutin; and (14) isoquercitrin.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

extract contains a high level of antioxidants compared to leaves extract. Further, the cyclic voltammetry method confirms the higher antioxidant activity of amaranth flower extract since it exhibited swift removal of active oxygen through a significant improvement in the electrochemical oxidation compared to the leaf extract of *A. hypochondriacus* (Kwon et al., 2019). Sarker and Oba (2020) studied the antioxidant activity of 11 genotypes of *Amaranthus hypochondriacus* using DPPH radical scavenging assay. All the genotypes exhibited antiradical activity, and 4 of the genotype, namely AHC4, AHC5, AHC6, AHC10, and AHC11, exhibited excellent antioxidant properties. The antioxidant activity of the methanol grain extract of *A. hypochondriacus* was studied using ABTS radical scavenging assay. The methanol grain extract exhibited good antioxidant activity against ABTS+ radical, and the IC_{50} value 19.1 mg/ml (Bhat et al., 2015). The antioxidant

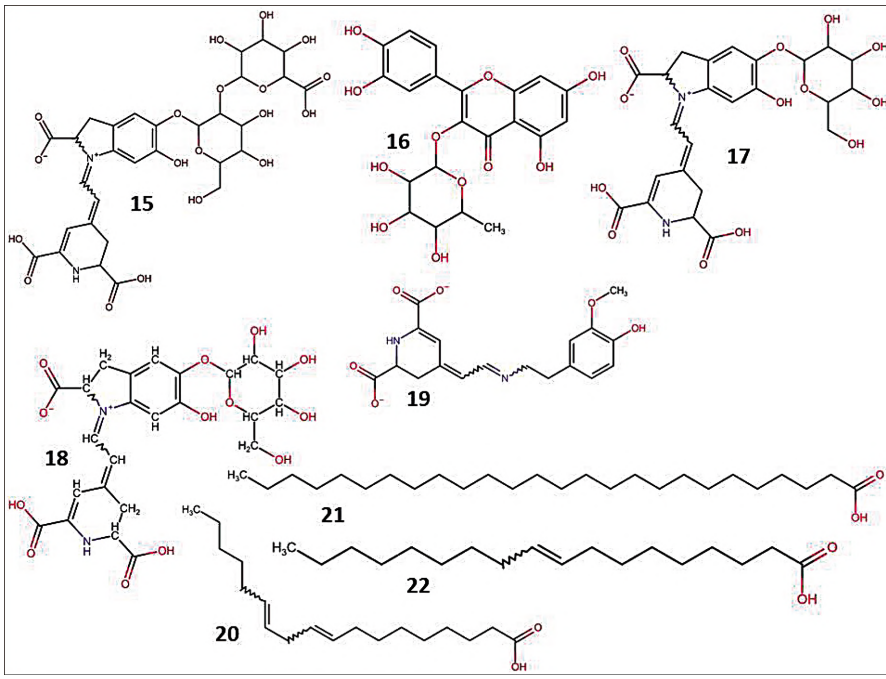


FIGURE 12.2 Bioactive compounds (phenols, flavonoids, fatty acids, and steroids) found in *A. hypochondriacus* – (15) amaranthin; (16) quercitrin; (17) betacyanin; (18) betalains; (19) betaxanthin; (20) linoleic acid; (21) hexacosanic acid; and (22) oleic acid.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

activity of methanol seed extract of *A. hypochondriacus* was studied using DPPH radical scavenging activity, NO scavenging activity, and β-carotene-linoleic acid assay. The results concluded that the antioxidant property is due to the presence of phenols, flavonoids, sterols, ascorbic acid, tocopherol, and carotenoids in the extract and the percentage of radical scavenging activity of *A. hypochondriacus* seed extract against DPPH radicals, NO radicals, and β-carotene was 86.93 ± 1.40, 35.20 ± 1.60, and 69.51 ± 1.50, respectively (López et al., 2011). The higher free radical scavenging activity of *A. hypochondriacus* was present in leaves than in seed, stalk, flower, and sprout extract. It was confirmed by performing oxygen radical scavenging activity (ORAC) and ferric-reducing antioxidant power (FRAP). The value of anti-radical activity for ORAC and FRAP was 451.40 µmol TE/g dry weight and 62.20 µmol AAE/g dry weight, respectively (Li et al., 2015). Oteri et al. (2021) studied the antioxidant property of four different accessions of *A. hypochondriacus* having different origins (India, Iowa, Pennsylvania, and

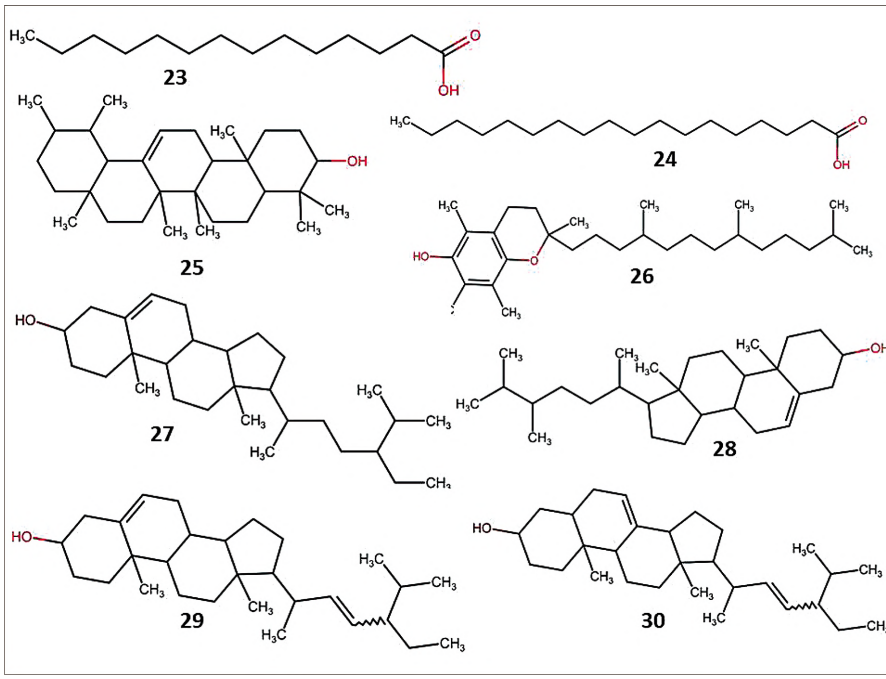


FIGURE 12.3 Bioactive compounds (phenols, flavonoids, fatty acids, and steroids) found in *A. hypochondriacus* – (23) myristic acid; (24) stearic acid; (25) α-amyrin; (26) α-tocopherol; (27) β-sitosterol; (28) campesterol; (29) stigmasterol; and (30) spinasterol.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

Nebraska) using DPPH and ABTS radical scavenging assay. The accession from Pennsylvania exhibited the highest antioxidant activity against DPPH radicals, followed by India, Nebraska, and Iowa. Similarly, the $ABTS^{+}$ radical scavenging activity exhibited by the Pennsylvania accession was higher than other accessions ranging from 1.75 to 2.22 µmol TE/g seeds.

12.3.2 ANTIFUNGAL ACTIVITY

The antifungal activity of *A. hypochondriacus* seed protein extract was studied against *Alternaria alternata, Candida albicans, Fusarium oxysporum, Trichoderma* sp., *Fusarium solani,* and *Aspergillus ochraceus.* The antifungal activity against *A. alternata, F. solani, F. oxysporum,* and *Trichoderma* sp. was determined by the "poisoned" agar method. The protein extract was most effective against *F. solani* with a mycelial growth of 6.0 mm, and it was least effective on *F. oxysporum* with mycelial growth of 30.8 mm. Further, the

antifungal activity of the protein extract against *C. albicans, F. oxysporum, A. ochraceus,* and *Trichoderma* sp. was determined using the microspectrophotometry method. *C. albicans* is the most sensitive against the seed protean extract with 100% growth inhibition, followed by *A. ochraceus* (ranging from 70–80% of growth inhibition) and *Trichoderma* sp. (ranging from 60–70% of growth inhibition). In contrast, it was the least effective against *F. oxysporum* with 35.15% of growth inhibition (Rivillas-Acevedo and Soriano-García, 2007a). Ay-AMP, an antifungal peptide isolated from the seed of *A. hypochondriacus* exhibits antifungal activity at a low dose against *Alternaria alternata, Penicillium chrysogenum, Aspergillus candidus, Candida albicans, Aspergillus ochraceus, Trichoderma* sp., *Geotrichum candidum,* and *Fusarium solani* (Rivillas-Acevedo and Soriano-García, 2007b). The amaranth seed extract exhibits antifungal activity against *Alternaria alternata, Aspergillus flavus,* and *Fusarium culmorum* by suppressing the growth and forming an inhibition zone of 1.0 cm, 1.2 cm, and 1.0 cm, respectively at a dose of 50 mg/ml (Mošovská and Bírošová, 2012).

12.3.3 HEPATOPROTECTIVE ACTIVITY

The hepatoprotective effect of *Amaranthus hypochondriacus* seed ethanol extract was studied on sodium arsenite-treated male Wistar rats. The rats treated with ethanol seed extract at 200 and 300 mg/kg body weight plus 2.5 mg sodium arsenite/kg body weight showed a significant decrease in the elevated levels of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, and alkaline transferase due to the toxicity of sodium arsenite. There was a significant increase in SOD, CAT, and GPx, which are considered biomarkers of antioxidant activity. Moreover, there is a reduction in the level of malondialdehyde (MDA), hydrogen peroxide (H_2O_2), and increased frequency of micronucleated polychromatic erythrocytes in bone marrow cells in the presence of *Amaranthus hypochondriacus* seed ethanol extract. Further, the histopathological study of the liver shows reduced toxicity. Thus, it was concluded that *Amaranthus hypochondriacus* mitigates the hepatotoxicity in Wistar male rats induced due to sodium arsenite (Akin-Idowu et al., 2015). The administration of *A. hypochondriacus* seed extract in alcohol-treated rats resulted in a significant reduction in MDA, AST, and NADPH oxidase transcript levels. Moreover, there is a significant increase in the expression of Cu, Zn-superoxide dismutase, and the activity of CAT and SOD, thus inducing hepatoprotective function in rats (López et al., 2011). Kasozi et al. (2018) also reported that intake of *A. hypochondriacus* grain supplementation by nicotinamide and streptozotocin

(STZ)-induced type 2 diabetes mellitus male Wistar rats exhibited hepato-protective activity by reducing the level of MDA and improving the activity of glutathione (GSH) peroxidase in rat hepatic cells as compared to the control group.

12.3.4 ANTICANCER ACTIVITY

Many reports suggest that the bioactive peptides isolated from amaranth show significant anticancer and anti-tumor activity. Silva-Sánchez et al. (2008) investigated the anticarcinogenic effect of lunasin, a peptide found in the seed of *A. hypochondriacus*; lunasin presence was identified in albumin, globulin, glutelin, and prolamin amaranth protein fractions. The tryptic-digested glutelin extract at five µg/ml induced 38.8% of apoptosis against HeLa cells, thus exhibiting its anticancer activity. This study indicated that lunasin present in glutelin extract could induce apoptosis in the neoplastic cells. Maldonado-Cervantes et al. (2010) reported that lunasin like peptide extracted from the protein fraction of the seed of *A. hypochondriacus* could be internalized into the NIH-3T3 cell nucleus and inhibit the acetylation of histones proteins and prevent the NIH-3T3 cells from transforming into cancerous cells. Further treatment with 500 and 1,000 nM of amaranth lunasin-like peptide reduces the viability of cells pretreated with carcinogen 3-methylcholanthrene (3-MCA). The saponin content of amaranth has cytotoxicity and anti-tumor properties (Mroczek, 2015). The peptides isolated from protein hydrolysates of amaranth seed is capable of inhibiting the growth of human triple-negative breast cancer cell by inducing apoptosis, membrane integrity loss, DNA fragmentation, translocation of phosphatidylserine and up-regulation of caspase-3 protein in the treated cells and inhibiting the migration of cells (Taniya et al., 2020).

12.3.5 ANTI-INFLAMMATORY ACTIVITY

Reports indicate that the bioactive peptides derived through amaranth grain (*Amaranthus hypochondriacus*) by the process of *in vitro* simulated gastrointestinal digestion of germinated amaranth exhibited anti-inflammatory activity against lipopolysaccharide (LPS)-induced inflammation in Murine Macrophage cell line that was established from a tumor in a male mouse induced with the Abelson murine leukemia virus (RAW 264.7) by significantly reducing the production of NO in the cell, used as a biomarker for inflammation response. Besides, the peptide fraction

of F1 (> 10 kDa) and F2 (3–10 kDa) at 0.5 mg/ml have enormously reduced the NO production by 65.2% and 66.6%, respectively, thus inducing an anti-inflammatory response in the macrophage cells (Sandoval-Sicairos et al., 2021). *Amaranthus hypochondriacus*, amaranth grain, contains soluble peptides that can inhibit mRNA expression responsible for the production of Chemokine (C-C motif) ligand 20 (CCL20), a chemotactic factor on mucosal and immune cells of the intestine exerting an anti-inflammatory effect in the colonic-epithelial cells (Moronta et al., 2016a, b). Amaranth hydrolysates obtained from *A. hypochondriacus* grain induced anti-inflammatory activity in human THP-1 macrophages (human monocytic cell line derived from an acute monocytic leukemia patient) and mouse RAW 264.7 macrophage cells. The hydrolysates induce anti-inflammatory by significantly reducing the expression of Tumor Necrosis Factor Alpha (TNF-α), which led to a reduction in the level of PGE2 (Prostaglandin E2) and COX-2 (Cyclooxygenase 2); moreover, it inhibits the phosphorylation of IκB kinase α (IKK-α). It causes the inactivation of IκB-α (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha), and all these lead to the inactivation of the NF-κb signaling pathway, which is responsible for the regulation of inflammation (Montoya-Rodríguez et al., 2014a). The biopeptide Ser-Ser-Glu-Asp-Ile-Lys-Glu (SSEDIKE), isolated from amaranth (*A. hypochondriacus*) grain, possesses anti-allergic properties. The peptide inhibited the allergic reaction in mice by suppressing the immunoglobulin E (IgE) secretion and inactivation of the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κb) signaling pathway, thus inducing tolerance to intestinal inflammation (Moronta et al., 2016a).

12.3.6 ANTI-DIABETIC ACTIVITY

Studies revealed that young leaf extract of *A. hypochondriacus* has anti-diabetic factors; the extract exhibited an inhibitory effect on the activity of α-amylase and α-glucosidase; the percent inhibition for the enzyme was 85.66 and 2.846, respectively (Aditya and Bhattacharjee, 2018). *A. hypochondriacus* hydrolysates contain globulin peptides that inhibit dipeptidyl peptidase IV (DPP IV) activity by binding at the enzyme dimerization site and inactivating its function. Thus, these peptides can act as an antihyperglycemic factor and regulate diabetes (Velarde-Salcedo et al., 2013). When Streptozotocin (STZ)-induced hyperglycemic rats were fed with amaranth grain, there was a significant reduction in the elevated level of DPP IV activity, inducing antihyperglycemic activity in rats (Velarde-Salcedo

et al., 2017). The albumin, globulin, and glutelin hydrolyzates isolated from *A. hypochondriacus* grain exhibited a significant inhibitory effect on DPPIV in STZ-induced diabetic mice. Among all the assessed glutelin hydrolyzates, GluH24 exhibited significant improvement in the glucose tolerance level with a remarkable increase in the level of plasma insulin, and it decreased the plasma glucagon level in the diabetic mice; thus, the bioactive peptides present in the amaranth grain has a potential antidiabetic effect (Soriano-Santos et al., 2015).

12.3.7 ANTI-HYPERTENSIVE ACTIVITY

Various studies were performed to determine the inhibitory effect of bioactive peptides on the angiotensin I-converting enzyme (ACE), which is the crucial enzyme for increasing blood pressure. The biopeptides isolated from *A. hypochondriacus* contain an ACE inhibitory effect. Quiroga et al. (2012) reported that the tetrapeptides, ALEP, and VIKP isolated from *A. hypochondriacus* had exhibited 90% ACE inhibitory activity. The bioactive peptides separated from *Amaranthus hypochondriacus* through enzymatically-assisted hydrolysis using alcalase and flavourzyme exhibited an antihypertensive effect; further, the peptide fraction has the highest ACE inhibitory effect. The higher bioactivity against ACE was shown by two the peptide fraction isolated from combined two-step continuous hydrolysis with IC_{50} values of 0.158 and 0.134; thus, the protein fraction of amaranth seed can help lower blood pressure (Ayala-Niño et al., 2019). De La Rosa et al. (2010) reported that trypsin-digested glutelins isolated from the amaranth were found to have an ACE inhibitory effect and can induce vasodilation by endothelial NO production in coronary endothelial cells 52% which is comparable to captopril and bradykinin, both used as control. Thus, trypsin-digested glutelins can be helpful in the prevention of cardiovascular diseases. Medina-Godoy et al. (2013) reported that after oral administration of biopeptides spontaneously, hypertensive rats exhibited hypertensive activity with a significant reduction in the mean arterial pressure and ACE inhibition. These results were similar to the captopril-treated group. The modified 11S globulin protein of amaranth showed higher inhibitory activity of the angiotensin-converting enzyme (IC_{50} 0.064 mg ml^{-1}). It was eight times more active than non-modified protein (Luna-Suárez et al., 2010).

12.3.8 ANTI-ATHEROSCLEROTIC ACTIVITY AND ANTITHROMBOTIC ACTIVITY

The peptides isolated from *Amaranthus hypochondriacus* exhibited anti-atherosclerotic activity by down-regulation of factors such as intracellular adhesion molecule-I (ICAM-I), Lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1) and matrix metalloproteinase-9 (MMP-9) in the LPS-induced THP-1 human macrophage-like cells. Further, the isolated bioactive peptides also exhibited a significant downregulation in the expression of pro-inflammatory and pro-atherosclerotic cytokines by 19–89% (Montoya-Rodriguez et al., 2014b, 2015b). The protein hydrolysates obtained by gastrointestinal digestion and activation of endogenous protease from *Amaranthus hypochondriacus* prevent the *in vitro* formation of fibrin clots. Moreover, the study of the parameter of the coagulation cascade suggests that amaranth protein has significant inhibitory effects on the coagulation phase of hemostasis. The study of activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) tests also revealed the antithrombotic activity of amaranth protein in rat models (Sabbione et al., 2016a–c).

KEYWORDS

- ***Amaranthus hypochondriacus***
- **antithrombotic activity**
- **dipeptidyl peptidase IV**
- **Feather amaranth**
- **ferric reducing antioxidant power**
- **intracellular adhesion molecule-I**
- **oxygen radical scavenging activity**

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CHAPTER 13

Bioactives and Therapeutic Potential of Red Root Pigweed (*Amaranthus retroflexus* L.) and Berlandier's Amaranth (*Amaranthus polygonoides* L.)

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13.1 INTRODUCTION

Amaranthus retroflexus L. is an annual herb and one of the most common weedy amaranth that is native to tropical America. It primarily grows in the riverbank of Eastern and Central USA, South-Eastern Canada, and Mexico (Sauer, 1967). A recent study reveals that the plant has a wide distribution in Asia, Europe, South America, and Africa (Pacifico et al., 2008). The plant is commonly called "Rough Pigweed" or "Redroot Pigweed" Amaranth. The amaranth has an erect stem of about 2 m with fine hairs, and it is freely branched. The leaves are rhombic-ovate and green in color with a long thin petiole and wavy or undulating margin (CABI, 2021). The inflorescence is greenish or crimson and clustered terminally; the flower is densely crowded and has green spiny bracts. The flowering occurs from July-September. The fruit is a utricle or a membranous bladder with a tiny black or dark brown

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oval seed. The root system contains pink or red short stout taproots (Walsh, 1993).

The redroot pigweed is generally used as fodder for sheep because of its nutrient composition and digestibility (Moyer and Hironaka, 1993). The young leaves are cut and cooked like spinach. The seeds are roasted and powdered to use as a substitute to cereals, and sprouted seeds are preferable in salads (Harrington, 1967; Hedrick, 1972). The plant is a rich source of iron, vitamin A and ascorbic acid (Allardice, 1993). The tea made from the young leaves of redroot pigweed treats profuse menstruation, intestinal bleeding and diarrhea (Foster and Duke, 1990; Moerman, 1998). The rough pigweed seeds with hull contain 18% of protein (National Research Council, 1971). In the Indian state of Kerala, the leaves are finely chopped and mixed with grated coconut, chili pepper, turmeric, and garlic to make a traditional dish called "*thoran*" (Fiorito et al., 2017). The *A. retroflexus* seed basic nutrition value and energy content was estimated in 100 grams of the dry grains *viz.*, Carbohydrates (47.21 g); Proteins (15.03 g); Lipids (7.77 g); Water (8.61 g); Dietary fibers (6.70 g); Ash (4.20 g); Nitrogen (2.46 g) and Phosphorus (4.62 g) (Woo, 1919).

Amaranthus polygonoides L. is an annual herb that originated in Argentina and is present in several parts of North America (Mosyakin and Robertson, 2003). It is commonly known as tropical amaranth, smartweed amaranth and Berlandier's amaranth. The stems are cylindrical, with 4–5 mm diameter, greenish to red with whitish streaks more or less straight on the central axis. The branchlets are erect or ascending. The leaf of this plant is entire or toothed, oblong-lanceolate, obtuse or acute and has a long petiole of 1.3 cm. The inflorescence is a compressed cyme of unisexual flowers (cymules), axillary. Fruit is a compressed utricle, indehiscent or dehiscent around the circumference (circumscissile) with the top tardily separated as a cap, one-seeded, somewhat oblong, 2–2.3 mm long.

The plant possesses good antioxidant, antimicrobial, and anticancer properties, and contains a good amount of protein and carbohydrates. It is rich in calcium, phosphorus, and iron. *A. polygonoides* extract consists of xanthophylls such as neoxanthin (12.5 mg), violaxanthin (2.41 mg), lutein (25.7 mg), zeaxanthin (1.19 mg) and total xanthophylls (41.8 mg) per 100 grams of the plant dry weight; provitamin-A signified by the presence of beta carotene (48.1 mg/100 g dry weight) with 3.43 retinol equivalents (RE) of green leafy vegetables (Sangeetha and Baskaran, 2010). The leaves are lightly sweet, regular consumption of *A. polygonoides* enhances appearance; it is beneficial in treating cough, eye disorders, problems in urination, ulcers,

and inflammation. Daily consumption of the cooked plant helps subjects with hemorrhoids, skin diseases like scabies and eczema (Sathiyaraj and Kumuthakalavalli, 2014).

13.2 BIOACTIVE COMPOUNDS

Many studies suggest that *Amaranthus* sp. leaf, root, seed, and flower extract contains numerous bioactive compounds which contribute to its pharmacology. Amaranth contains bioactive peptides, flavonoids, phenols, alkaloids, steroids, organic acids, fatty acids, terpenoids, and nitrogen-containing compounds as major phytochemical constituents. Noori et al. (2015) reported flavonoids in different parts of *A. retroflexus,* including quercetin, rutin, kaempferol, myricetin, and chrysin, isorhamnetin, vitexin, morin, amaranthin, and apigenin. Further, flavonoid sulfate, flavone *C* and *C-/O* glycosides and aglycons are present in the root and aerial part of amaranth. Pacifico et al. (2008) investigated the total phenol content of *A. retroflexus* leaves, which was 0.014 mg/g of dry material. *A. retroflexus* contains polyhydroxylated nerolidol, such as sesquiterpene (amarantholidols A, B, C, and D) and glucosides (amarantholidoside I, II, IV, V, VI, and VII). Different parts of *A. retroflexus* contains sesquiterpene glucosides namely nerolidol glucosides, amarantholidosides, and amarantholidols (Fiorentino et al., 2006). The edible part of *A. retroflexus* contains prenylpropanoids such as ferulic acid, umbelliferone, apigenin, boropinic acid, auraptene, umbelliprenin, isopentenyloxycoumarin, and 4-Geranyloxyferulic acid (Fiorito et al., 2017). The ethanol leaf extract of *A. retroflexus* contains tannins, phytosterols, flavonoids which contribute to its antioxidant activity (Jain and Setty, 2016). Flath et al. (1984) reported the presence of volatile constituents in *A. retroflexus*, and a few of them are acetaldehyde, hexanol, dimethyl sulfide, 3-methylbutanal, trans-2-hexenyl acetate, trans-2-hexanal, cis-3-hexenyl propionate, 3-hexen-1-ol and 3-methylbutan-1-ol. The volatile organic compound mixture released by hydro extract of *Amaranthus retroflexus* plant tissue was examined using GCMS. The headspace profile was found to alter significantly with time; high quantities of hexanal were discharged shortly after the formation of the mixed suspension, along with minor quantities of five- and six-carbon oxygenated compounds. A fresh plant sample was combined with water, more hexanal, lesser amounts of trans-2-hexenal, and small quantities of 3-pentanone, 1-penten-3-ol, cis-3-hexen-1-ol, l-penten-3-one and copious minor components were observed. When the blended substance was allowed to stand for several hours, the

hexanal headspace concentration reduced by a factor of 2.5, while trans-2-hexenal, cis-3-hexen-1-01, and the other ingredients persisted relatively constant. The hexanal concentration continued to decrease with time; after 12 hours of storage, the mixed *A. retroflexus* tissue produced a headspace profile comprising hexanal as a minor component. Trans-2-hexenal was the significant constituent cis-3-hexen-1-01 concentration increased slightly (Flath et al., 1984). The ingredient and fatty-acid proportions of phospholipids, neutral lipids (NL), squalene, and glycolipid content in seeds and the aerial part of *A. retroflexus* were studied. The presence of elaidic acid was witnessed in all lipid groups. The squalene content was 4.30% of the NLs mass in *A. retroflexus* seeds and 3.15% in the aerial portion (Ibotov et al., 2021).

The study of phytochemical constituents of *A. polygonoides* indicates different bioactive compounds like flavonoids, steroids, alkaloids, anthraquinones, cardenolide, tannins, saponins, and reducing sugar. These compounds make the plant a potential therapeutic agent (Sivagnanam et al., 2014). The grains obtained from *A. polygonoides* have higher protein content (11–17%) than most cereal grains. The grain of *Amaranthus* species is a potent alternate for people who are allergic to gluten as the gluten content is significantly less and hence often regarded as pseudocereals (Mlakar et al., 2009). Amaranth protein contains a high amount of albumins and globulins which make it a potent grain for the production of flour, moreover, it is gluten-free and has a negligible amount of prolamins which make it an important nutrient-rich plant product (Singh et al., 2019). The important flavonoids present in *A. retroflexus* is given in Figures 13.1–13.3 and the important bioactive compounds present in *A. polygonoides* is given in Figure 13.4.

13.3 PHARMACOLOGY

13.3.1 ANTIOXIDANT ACTIVITY

Hydroxyl radical scavenging activity of 70% ethanolic extract of *Amaranthus retroflexus* leaves (AREE) was investigated. The results reported that the hydroxyl scavenging activity of *A. retroflexus* leaves extract showed a better scavenging activity of 58.064%. The *in vitro*-antioxidant activity by ethanolic extract of *A. retroflexus* leaves (AREE) was found due to antioxidant phytochemicals like phytosterols and flavonoids, and other polyphenolic constituents (Jain and Setty, 2016). The free radical scavenging activity of

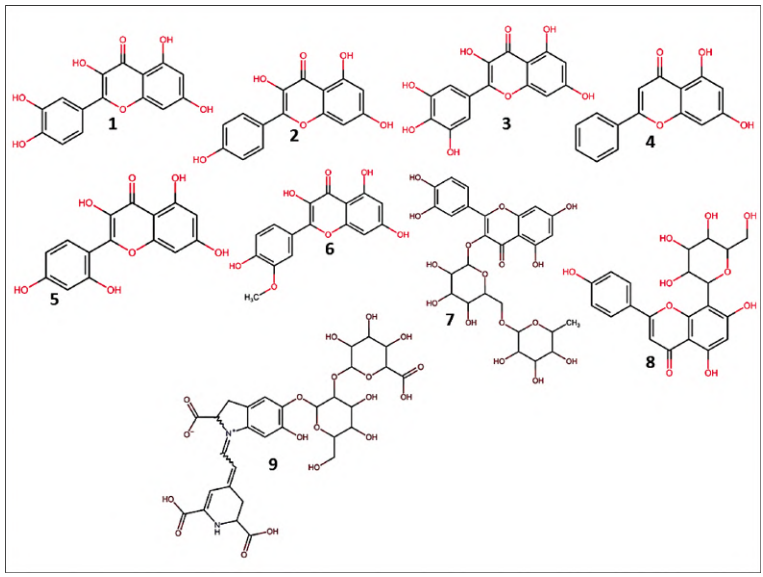


FIGURE 13.1 Flavonoids present in *A. retroflexus* – (1) quercetin; (2) kaempferol; (3) myricetin; (4) chrysin; (5) morin; (6) isorhamnetin; (7) rutin; (8) vitexin; and (9) amaranthin.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

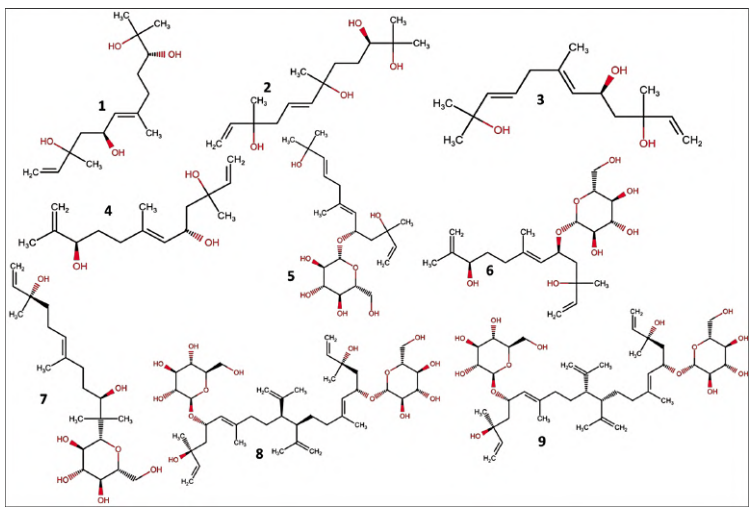


FIGURE 13.2 Sesquiterpenes and Glucosides found in *A. retroflexus* – Sesquiterpenes *viz*., (1) Amarantholidol A; (2) Amarantholidol B; (3) Amarantholidol C; (4) Amarantholidol D; Glucosides viz., (5) Amarantholidoside I; (6) Amarantholidoside II ; (7) Amarantholidoside IV; (8) Amarantholidoside V; and (9) Amarantholidoside VII; [Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures].

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

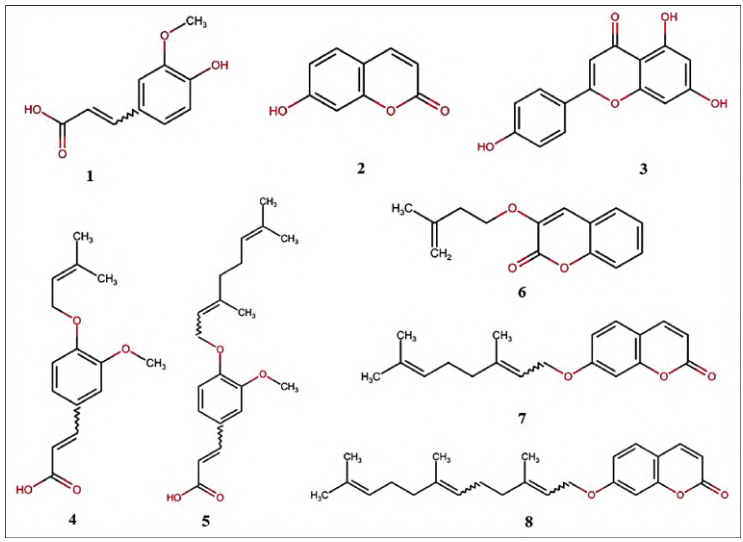


FIGURE 13.3 Prenylpropanoids found in *A. retroflexus* – (1) ferulic acid; (2) umbelliferone; (3) apigenin; (4) boropinic acid; (5) 4-geranyloxyferulic acid; (6) isopentrnyloxycoumarin; (7) auraptene; and (8) umbelliprenin.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

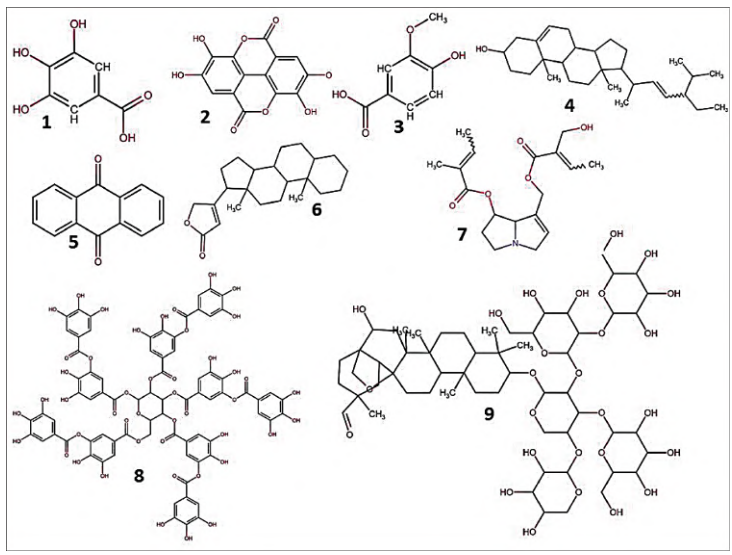


FIGURE 13.4 Important bioactive compounds present in *Amaranthus polygonoides* – (1) gallic acid; (2) ellagic acid; (3) vanillic acid; (4) stigmasterol; (5) anthraquinone; (6) cardenolide; (7) alkaloid-A; (8) tannin; and (9) saponin.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

A. retroflexus was studied by DPPH radical scavenging assay, and the total phenol content was estimated by the Folin-Ciocalteau method. The crude extract was added to the alcohol solution of free radical DPPH at various concentrations (20, 50, 75, 100, 150, and 200 mg). It was observed that after 30 min incubation, the lowest tested dose exhibited a significant reduction of free radical by 18.8%. The highest tested dose of the crude extract exhibited the reduction of total free radicals by 73.3%. The recorded IC_{50} value for *A. retroflexus* methanol extract was found to be 92.7 mg/ml. In the H_2O_2 radical scavenging assay, the scavenging power of *A. retroflexus* was found to be 73% as compared to standards ascorbic acid and a-tocopherol, which was found to be 75% and 58%, respectively. It was observed that methanolic extract of *A. retroflexus* exhibited an intense antioxidant activity. The nerolidol compound derivatives displayed good antiradical activity compared to the standard a-tocopherol (Pacifico et al., 2008).

The antiradical property of *A. polygonoides* leaf extracts was determined by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. *A. polygonoides* aqueous leaf extract was found to be 84% in comparison to the free radical scavenging activity of vitamin C, which recorded 66.2%. Further, the superoxide anion inhibition activity of the aqueous leaf extract of *A. polygonoides* is 93.9% in comparison to vitamin C which is 83.4% (Naveena et al., 2012). Moreover, Naveena et al. *(*2012) also studied nitric acid scavenging activity of *A polygonoides* leaf extract compared to Vitamin C at different concentrations. The plant's leaf extract exhibited the highest level (71.8%) of nitric oxide (NO) scavenging activity at the concentration of 500 µg/ml compared to vitamin C at a similar concentration.

13.3.2 ANTIMICROBIAL ACTIVITY

It was reported that the growth of different pathogenic fungi could be restricted by the peptide Ar-AMP isolated from *A. retroflexus*. It was observed that *Fusarium culmorum* was highly susceptible to Ar-AMP peptide. It was observed that *Alternaria consortiale* is the least effective fungi. In contrast, no growth inhibition was reported by Ar-AMP peptide on *Rhizoctonia solani*, the development of sclerotia around the wall was affected (Lipkin et al., 2005). It was reported that different parts of the plant *A. retroflexus* possess antimicrobial activity against bacteria and fungi. The chloroform seed extract of *A. retroflexus* was found to be most effective against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*

by forming an inhibition zone of 18 ± 0.4 mm, 20 ± 0.1 mm, 20 ± 0.3 mm, 19 ± 0.4 mm and 28 ± 0.4 mm, respectively. The aqueous extract and ethanol extract of aerial part and root of *A. retroflexus* were independently found to be effective against *Staphylococcus aureus* and *Candida albicans* (Poiata et al., 2016). The ethanolic root extract of *A. retroflexus* showed antimicrobial activity against mycotoxigenic fungal strains viz., *Aspergillus ochraceus, Fusarium graminearum, Penicillium verrucosum, Aspergillus niger,* and *Penicillium expansum* by forming inhibition zone of 9.7 ± 0.3 mm, 14.2 ± 0.1 mm, 11.0 ± 0.04 mm, 12.8 ± 2.2 mm and 9.5 ± 0.03 mm, respectively. The methanolic extract of leaf and stem extract shows significant antifungal activity against *A. ochraceus, F. graminearum, P. verrucosum, A. niger,* and *P. expansum* by forming inhibition zone of 11.0 ± 0.04 mm, 9.7 ± 0.02 mm, 9.2 ± 0.06 mm, 11.3 ± 0.2 mm and 9.7 ± 0.3 mm, respectively (Terzieva et al., 2019).

The antibacterial and antifungal property of *A. polygonoides* aqueous leaf extracts at different concentrations (50, 100, and 150 µg/disc) was analyzed compared to standard antifungal and antibacterial drugs like ketoconazole and ciprofloxacin, respectively. The plant extracts effectively inhibited *Staphylococcus aureus, Staphylococcus epidermidis, Micrococcus luteus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Aspergillus niger,* and *Aspergillus fumigatus* at a different concentration by forming a zone of inhibition (Naveena et al., 2012). It was reported that the AgNPs obtained from aqueous extract of *A. polygonoides* exhibited significant antifungal activity against *Candida albicans* and *Saccharomyces cerevisiae* at a different concentration by forming a zone of inhibition. It was observed that at 1,000 µg the zone of inhibition was found to be 10 mm and 9 mm for *C. albicans* and *S. cerevisiae*, respectively (Firdhouse and Lalitha, 2015).

It was reported that aqueous extract of *A. polygonoides* fresh leaves can be used to synthesis silver nanoparticles by the application of the conventional method, high-temperature method and sonication method. The shape of silver nanoparticles obtained from the plant extract was found spherical and the size was found to be less than 50 nm. The characterization of the nanoparticles was done using XRD analysis, SEM analysis, UV-visible spectra analysis and FTIR (Fourier transform infrared spectroscopy) analysis (Firdhouse and Lalitha, 2013). It was further reported that the biogenic AgNPs can be synthesized by application of sonication method on aqueous extract of *A. polygonoides*. The characterization of the silver nanoparticle was done using TEM analysis and it was found that the size of the AgNPs was ranging

from 5–25 nm. It was reported that the AgNPs showed significant antifungal activity (Firdhouse and Lalitha, 2015).

13.3.3 CYTOTOXIC ACTIVITY

The percentage of yield of fatty acids in *Amaranthus retroflexus* plant extract consists of linoleic acid (4.19 ± 0.35) and linolenic acid (3.71 ± 0.29). The percentage yield of total phenols from the hydro-alcoholic extracts of *A. retroflexus* is 15% and total phenolics content using Folin–Ciocalteau method is 59.0 ± 0.9 mg/g (Chlorogenic acid equivalents). The IC_{50} values of free radical scavenging activity on DPPH of *A. retroflexus* is 510 ± 3.2 µg/ml. This study investigated whether *A. retroflexus* accentuates NO's generation by the RAW 264.7 mouse macrophage cell line pre-treated with plant extracts (1,000 µg/ml) before activation by bacterial lipopolysaccharide (LPS). The exposure of RAW 264.7 macrophages with LPS (1 µg/ml) for 24 hours provokes NO production, which can be quantified by employing the chromogenic Griess reaction, which measures nitrite accumulation, a stable metabolite of NO. The beneficial effect of the plant extract on the quenching inflammatory arbitrators in macrophages can be propitiated by oxidative degradation of phagocytosis products, such as $O^{\cdot -2}$ and HOCl. Incubation of RAW 264.7 cells with extracts from non-cultivated *A. retroflexus* (leaves) induced a remarkable inhibitory influence on the LPS-induced nitrite generation in a concentration-dependent mode with an IC_{50} value of 56 µg/ml. This action is similar to the standard drug indomethacin (IC_{50} value of 58 µg/ml) (Conforti et al., 2011). The *A. retroflexus* extract has been tested for cytotoxicity against bovine kidney cells and bioactivity in *Artemia salina*. For the bioactivity in *Artemia salina*, the regression method was used to analyze LC_{50} values in the *Artemia salina* by following the brine shrimp test. For *Artemia salina* the reported LD_{50} value was 1,700 ppm. Different concentrations of the plant extracts from 100 ppm–0.1 ppm were used to treat bovine kidney cells for determining cytotoxic activity with plant extract of *A. retroflexus*. The cytotoxicity study was carried out following the MTT viable assay. It was observed that the cell viability decreased to about 49% and 35% after treating with 100 and 0.1 ppm concentrations for 24 h. The results suggested that extract of *Amaranthus retroflexus* was non-toxic for *Artemia salina* but has shown direct toxicity against bovine kidney cells (Amoli et al., 2009).

13.3.4 ANTIFUNGAL ACTIVITY OF A. RETROFLEXUS SYNTHESIZED SILVER NANOPARTICLES

The antifungal activity of *A. retroflexus* synthesized AgNPs was tested for fungi *Alternaria alternata*, *Macrophomina phaseolina*, and *Fusarium oxysporum*. It was observed that *A. retroflexus* synthesized AgNPs effectively reduced the growth of three fungal species compared to the negative control. At 400 mg/ml of the *A. retroflexus* synthesized AgNPs, the highest inhibition rate of 71.09% ± 1.41% was reported in fungi *M. phaseolina*. The lowest inhibition rate of 9.84% ± 2.81% was observed in *F. oxysporum* at 50 mg/ml of the *A. retroflexus* synthesized AgNPs. The biosynthesized AgNPs at 50 mg/ml concentration induced 31% inhibition of the growth in *M. phaseolina*. It was observed that the AgNPs had shown fragile antifungal activity against fungi *Trichoderma harzianum*. There was no antifungal effect seen against *Geotrichum candidum*. The study also reported minimum inhibitory concentration values of the AgNPs that were found to be 159.80 ± 14.49, 337.09 ± 19.72, and 328.05 ± 13.29 mg/ml against fungi *M. phaseolina*, *A. alternata* and *F. oxysporum*. According to the statistical analysis data, no difference was reported in minimum inhibitory concentration between *F. oxysporum* and *A. alternata*. At the range of the tested concentrations, no minimum inhibitory concentration of AgNPs was observed for *T. harzianum* and *G. candidum*. Based on the findings, the results suggested that the most sensitive and resistant microorganisms to the *A. retroflexus*-synthesized AgNPs were *M. phaseolina* and *G. candidum* (Bahrami et al., 2017).

13.3.5 RENAL TOXICITY

Around 41 pigs were administered with pigweed (*Amaranthus retroflexus)*. Out of 118 pigs given with *A. retroflexus*, 15 exhibited clinical symptoms of perirenal edema, and all 18 had gross sores usually seen in pigs with perirenal edema. Changes in few biochemical values and electrolyte conditions in blood were observed in swine given with *A. retroflexus* extract; there was a significant and steady increase in serum K and a more modest rise in serum Mg, including an increase in blood urea. Microscopical lesions involved dilatation of convoluted and collecting tubules, the emergence of proteinaceous tubular casts, necrosis, and renal tubular degeneration, changes on the electrocardiogram pattern in eight *A. retroflexus* extract-treated pigs, similar changes were observed in pigs with excess serum K presented experimentally in control animals (Osweiler et al., 1969).

KEYWORDS

- ***Amaranthus retroflexus***
- **cytotoxic activity**
- ***Amaranthus polygonoides***
- **neutral lipids**
- **renal toxicity**
- **silver nanoparticles**

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CHAPTER 14

Phytochemicals and Pharmacological Potential of *Acampe ochracea* and *A. praemorsa* (Orchidaceae): An Overview

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14.1 INTRODUCTION

The term *Acampe* originates from the Greek *acampes* (rigid), which refers to its overall character pertaining to all aerial parts of the plant. The genus comprises robust monopodial epiphytic orchids with coriaceous leaves and rigid flowers on a short raceme. There are over 10 species of *Acampe* distributed in India, South Africa, Sri Lanka, Southern China, the Philippines, and Southeast Asia (Prasad et al., 2019). In this chapter, a comprehensive review has been given on bioactive compounds and pharmacological potentiality of *Acampe ochracea* and *A. praemorsa*.

14.2 *A. OCHRACEA* (LINDL.) HOCHR.

Acampe ochracea is an epiphyte growing on tree trunks in open forests or at forest margins. It is distributed in Bhutan, Thailand, Cambodia, Malaysia, Laos, Myanmar, Sri Lanka, and Vietnam. In India, it is found in North-East India, Kerala, and Andhra Pradesh. Synonyms of this plant include *Acampe dentata* Lindl.; *A. griffithii* Rchb.; *Gastrochilus ochraceus* (Lindl.) Kuntze.

Epiphytic orchid. Leaves are 16–19 × 2 cm oblong, keeled, obliquely bilobate at apex. Flowers are yellow, 1.5 × 1.5 cm in 10–20 cm long, axillary panicles, dorsal sepal 7 × 2 mm, obovate, obtuse, 5-veined lateral sepals 6 ×

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1–2 cm, obliquely oblong, acute, 5-veined, petals 7 × 1–2 mm, obovate-oblong or spatulate, 6 veined, lip 4 × 2 mm, triangular, obtuse, papillate, with 5 × 1 mm cylindrical spur. It comes to flowering during February-April in India.

14.2.1 PHYTOCHEMICALS

Jhansi (2019) studied the GC-MS analysis of ethyl acetate (EA) extract of *A. ochracea*. Leaf EA extract showed the different organic compounds in typical gas chromatogram. Their peak area percentage, retention time and molecular mass were shown in Table 14.1. Among them major compounds were Tetracosane and Heptadecyl 3-chloropropanoate. In case of methanolic leaf extract, different chemical compounds were recorded in typical gas chromatogram. Their peak area percentage, retention time and molecular mass were shown in Table 14.1. The major compounds reported here were 2-Naphthalenemethanol, decahydro-α,α,4a-trimethyl-8-methylene-, [2R-(2α, 4aα,8aβ)]-and (1R, 4E, 9s)-4,11,11-Trimethyl-8-methylidenebicyclo[7.2.0]undec-4-ene. Here, in both EA and methanol extracts salicyl acyllucuronide, eicosane 7-hexyl were recorded. A total of 24 compounds recorded from *A. ochracea*.

14.2.2 ETHNOBOTANY AND PHARMACOLOGICAL POTENTIALITY

14.2.2.1 Anticancer Activity

Jhansi (2019) studied the *in vitro* cytotoxicity effect of *A. ochracea* leaf extracts against cancer cell lines, such as MCF-7 (breast cancer) and HeLa (cervical cancer) using MTT assay. In this study, the highest *in vitro* toxicity was recorded in methanolic extract against MCF-7 cells with least IC_{50} 22.53 µg/ml which was enough to kill 50% of MCF-7 cancer cells. Poor *in vitro* cytotoxicity was observed in EA extract against HeLa cell lines with an IC_{50} value 44.487 µg/ml.

14.2.2.2 Antimicrobial Efficacy

Paul et al. (2013) conducted the antibacterial assay with paper disk method. Water extract of *A. ochracea* showed remarkable activity against *E. coli* (Kanamycin resistant strain) with 7.0 mm diameter of inhibition zone. They further claimed that the presence of alkaloids in this orchid might be the reason for this efficacy.

TABLE 14.1 Chemical Compounds Recorded from Ethyl Acetate and Methanolic Extracts of *Acampe ochracea*

Extract	Name of the Compound	Peak Area (%)	R.T (min)	Mol. Mass (gms/mol)
Ethyl acetate	Salicyl acyl glucuronide	4.14	3.7167	314.24
	Trans-anethole	6.10	8.2000	148.20
	7-Chloro-5-phenyl-1-(trimethylsilyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one	3.96	9.0667	342.89
	2,3,3-Trimethyl-2-(3-methylbuta-1,3-dienyl)-6-	9.22	10.8333	218.33
	methylenecyclohexanone			
	4,8-Methano-1H-2-benzopyran, octahydro-8-methyl-9-methylene-5-(1-methylethyl)	3.64	11.5167	220.35
	1,2-Benzenedicarboxylic acid, butymethylpropyl ester	3.24	13.7500	278.34
	3-Deoxy-d-mannoic lactone	5.21	14.3667	162.14
	1-Butanol, 3-methyl-, acetate	4.68	17.7000	130.18
	Heptadecyl 3-chloropropanoate	10.47	26.2167	346.98
	Tetracosane	15.24	36.2333	338.66
	Methyl petroselinate	7.98	41.2833	296.49
	Lanosta-8,24-dien-3-ol	1.11	43.0333	426.72
	7-hexyl-eicosane	2.35	52.0333	366.71
Methanol	2-Naphthalenemethanol, decahydro-α, α,4a-trimethyl-8-methylene-, [2R-(2α,4aα,8aβ)]-	14.49	5.9167	222.36
	Salicyl acyl glucuronide	7.16	2.7000	314.24
	3,5-Dihydroxy-2,3-dihydropyran-4-one	2.44	7.7333	130.09
	Heptanoic acid, 6-oxo-	2.93	12.6667	144.17
	(E, E)-2,4-decadienal	4.24	14.0167	152.23
	(1R,4E,9S)-4,11,11-Trimethyl-8-methylidenebicyclo[7.2.0]undec-4-ene	19.00	9.667	204.35
	Hexadecanoic acid	1.30	21.1167	256.43
	(2E)-2-Morpholin-4-yliminoacetaldehyde	1.44	24.3333	142.15
	Eicosane, 7-hexyl-	8.26	34.2833	366.70
	Apoatropine	2.83	42.5833	271.36
	Cyclopropane carboxylic acid	6.89	47.9500	86.09

Jhansi (2019) evaluated the antimicrobial potential of leaf extracts (EA and methanolic extracts) of *A. ochracea* against gram-negative and gram-positive bacteria. Methanolic extract showed the highest zone of inhibition, 22 mm against *Enterococcus faecalis* and lowest against *Lactobacillus acidophilus*. It is followed by EA showing the 17 mm zone of inhibition against *L. acidophilus.*

14.3 *ACAMPE PRAEMORSA* (ROXB.) BLATT. AND MCCANN

A. praemorsa is distributed in Bhutan, Myanmar, Seychelles, and Sri Lanka. In India, it is in Eastern Ghats of Andhra Pradesh, Simlipal forests of Orissa, Arunachal Pradesh, Karnataka, Tamil Nadu, Kerala, Meghalaya, Mizoram, Nagaland, Sikkim, and West Bengal (Prasad et al., 2019). Synonyms of this species include *Acampe papillosa* Lindl. and *A. wightiana* (Lindl. ex Wight) Lindl. Vernacular names of this species are: Indian names: Marabale (in Canarese dialect); Maravasha, Khanbher, Nakul, Rasna (Marathi); Taliyamaravada (Malayanam), Kano-kato (Orissa), Gandhata (Sanskrit, Malayanam); Chinese name: Duanxucui Lan; Myanmar name: Mee ma long pan (Teoh, 2016).

A. praemorsa is a monopodial epiphyte with a stout stem, up to 30 cm long, 1–1.5 cm in diameter, leaves distichous, coriaceous, channeled, and unequally bilobed, ca. 25 × 3.5 cm size. Inflorescence is shorter than leaves, leaf opposed or supra-axillary, simple or rarely branched, nearly 10 cm long; fragrant flowers yellow, spotted with crimson; the lip white and sparsely speckled with magenta to dark brown.

14.3.1 PHYTOCHEMICALS

A. praemorsa contains flavidin and phenanthropyran known as Praemorsin (Anuradha and Prakasarao, 1994a, b). Akter et al. (2018) also detected the glycosides, flavonoids, saponins, tannins, terpenoids, steroids, coumarins, and anthraquinones.

Jhansi (2019) studied the GC-MS analysis of EA leaf extract of *A. praemorsa*. It showed the presence of various compounds and their peak area percentage, retention time, and molecular mass were given in Table 14.2. The major compounds recorded are 2-nonylmalonic acid and 3-Acetylylthio-2-methyl propionic acid. Similarly, in methanolic extract also various compounds have been reported (Table 14.3). Among them, the major compounds are 2,6,6,9-tetramethyl-1-1, 4-8-cycloundecatriene and Eudesm-4(14)-en-11-ol. A total of 35 compounds reported from this plant.

TABLE 14.2 Chemical Compounds Recorded from Ethyl Acetate Extract of *Acampe praemorsa*

Sl. No.	Name of the Compound	Peak Area (%)	R.T (Min)	Mol. Mass (gms/mol)
1.	Hydroperoxide,1-methylpentyl	3.40	2.6167	118.1742
2.	2,2,4,4,6,6,8,8,10,10,12,12-Dodecamethylcyclohexasiloxane	1.19	3.2333	444.924
3.	Oxalic acid monomethylester chloride	1.09	3.9333	139.511
4.	Hexanoic acid	9.36	5.5667	116.161
5.	4-(3-Hydroxybutyl) phenol	2.46	5.9833	166.22
6.	2-Hexyl-1-octanol	2.29	6.4167	214.393
7.	1,1-Methyl decahydronaphthalene	7.30	7.0167	152.281
8.	Octadec-9-enoic acid	2.16	10.0667	282.468
9.	3-Acetylthio-2-methylpropionic acid	12.24	12.0267	162.203
10.	(E,E)-2,4-decadienal	2.16	13.0167	152.237
11.	2-Nonylmalonic acid	12.14	14.1167	258.354
12.	Butanoic acid, pentyl ester	2.52	14.6333	158.241
13.	2-Methylhexadecan-1-ol	4.33	16.6167	256.474
14.	5-(Hydroxymethyl)-2-furaldehyde	2.29	18.3333	126.111
15.	5-methyl-furan-2-carbaldehyde	6.13	25.9833	110.112
16.	5-Pentadecylresornicol	2.53	27.0333	320.517
17.	7,11,15-Trimethyl-3-methylidenehexadec-1-ene	2.29	31.1167	278.524
18.	Octadeca-9,12,15-trienoic acid	3.49	44.6167	278.436
19.	3-Hydroxypropyl(9E)-9-octadecenoate	12.00	49.9500	398.300

14.3.2 ETHNOBOTANY AND PHARMACOLOGICAL POTENTIALITY

A decoction of roots of *A. praemorsa*, known as Rasna, is a bitter tonic, considered to be a remedy for rheumatism in India (Caius, 1936; Rao and Sridhar, 2007). It is also used for the treatment of sciatica, neuralgia, syphilis, and uterine disorders (Table 14.4).

In Eastern Ghats of Andhra Pradesh, India, the Koya community uses the pulverized plant, mixed with white egg yolk and calcium, for the treatment of fractured limbs to promote healing (Akarsh, 2004). The Dongira Kandha tribe of Niyamgiri Hills, Southeastern Orissa has been taking the teaspoon of paste prepared from *A. praemorsa* roots and *Asparagus racemosus* on empty stomach to relieve arthritic pains (Dash et al., 2008).

TABLE 14.3 Chemical Compounds Recorded from Methanolic Extract of *Acampe praemorsa*

Sl. No.	Name of the Compound	Peak Area (%)	R.T (Min)	Mol. Mass (gms/mol)
1.	Benzoic acid, 2,5-bis(trimethylsiloxy)-, trimethylsilyl ester	7.32	4.8167	70.66
2.	(1r,4ar,7r,8ar)-7-(2-hydroxypropan-2-yl)-1,4a-methyldecahydronaphthalen-1-ol	2.47	5.9167	40.38
3.	2-N-Butylthiophene	1.49	6.6333	140.25
4.	Benzene, 1,2-dimethyl-4-nitro-	4.36	10.8167	151.16
5.	2-Naphthalenemethanol, 1,2,3,4,4a,5,6,7-octahydro-.α, α,4a,8-tetramethyl-, (2R-cis)-	2.34	14.0167	222.36
6.	4-Methyl-2-pentyl acetate	2.64	15.1167	144.21
7.	Heptanoic acid, 6-oxo-, ethyl ester	12.35	15.2500	72.22
8.	(4aS,7R)-7-(2-hydroxypropan-2-yl)-1,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one	0.93	15.6000	236.35
9.	2,4-Di-tert-butylphenol	6.10	18.8833	206.32
10.	2,6,6,9-Tetramethyl-1,4-8-cycloundecatriene	19.32	21.7333	204.36
11.	Phthalic acid, butyl 8-chlorooctyl ester	1.00	21.8167	368.89
12.	Aromadendrene oxide-(2)	6.45	26.6333	220.35
13.	Methyl β-D-ribofuranoside	2.53	27.0167	164.16
14.	1-(3-Methylfuran-2-yl)propan-2-one	1.16	29.7500	138.16
15.	Eudesm-4(14)-en-11-ol	13.63	39.3137	222.37
16.	10-Heneicosene	1.91	42.8833	294.55

The tribal communities (bagali, chakma, marma communities) in South-East Bangladesh have been using leaves and whole plants of *A. praemorsa* for treating fever, earache, injury, and, male, and female problems (Akhter et al., 2017). In Nepal the powdered roots of *A. praemorsa* is consumed to treat rheumatism (Subedi et al., 2013). Vibha et al. (2019) admitted that *A. praemorsa* is a promising candidate for its pharmacological potential.

14.3.2.1 Anticancer Activity

In vitro cytotoxic effect of *A. praemorsa* against cancer cell lines was studied by Jhansi and Khasim (2020). In this study, MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay for the cytotoxicity assessment of the EA and methanol leaf extracts of *A. praemorsa* has been carried out on two different cell lines, MCF-7 (breast cancer) and HeLa (cervical cancer)

TABLE 14.4 Ethnobotanical importance of *A. praemorsa*

Region	Part used	Administered form	Therapeutic importance	References
Jamalpur (Bangladesh)	Roots	crushed roots used as tonic	Treatment of rheumatism	Hossain (2009, 2011)
Feni district (Bangladesh)	Leaf	Juice	Rheumatism, cough, ear complaints	Uddin et al. (2015)
South-East Bangladesh	Leaf and whole plant	-	Fever, earache and other female problems	Akhter et al. (2017)
Nepal	Root	Powder	Rheumatism	Subedi et al. (2013)
Sikkim (India)	Root	Paste, Decoction	Neuralgia, traumatic pain, arthritis, rheumatism, backache, menstruation pain, sciatica	Panda and Mandal (2013)
Nagaland (India)	Root	Paste	Burning sensation, asthma, bronchitis, secondary syphilis, mild uterine diseases, eye diseases	Nongdam (2014)
Meghalaya (India)	Root	Juice	As a tonic and for treatment of rheumatic disorders	Singh and Borthakur (2011)
Madhya Pradesh (India)	Root	Decoction	Cough	Tiwari et al. (2012)
Southeastern Orissa (India)	Root	Paste	Arthritis	Dash et al. (2008)
Kerala (India)	Leaf	-	Shampoo	Kumar et al. (2014)
	Seed, Leaf	Juice	Stomachache, earache, body temperature control, antibiotic for wounds	Shanavashkhan et al. (2012)
Mallapuram (Kerala)	Whole plant	Extract	Rheumatism	Chithra and Geetha (2016)
Tamil Nadu (India)	Root	Paste	Arthritis	Devi et al. (2015)
Andhra Pradesh (India)	Whole plant	-	Fracture	Reddy et al. (2005)
	Whole plant	Pulverized plant mixed with egg yolk and calcium	Treatment of fractured limbs	Akarsh (2004)

cell lines. Results showed that MCF-cell lines were more prone to death to EA extract with IC_{50} value of 49.276 µg/ml. This is enough to kill 50% of MCF-7 cancer cells, whereas poor cytotoxicity was recorded in methanolic extract against HeLa cell line (Jhansi and Khasim, 2020). Soumiya et al. (2018) evaluated the cytotoxic effect of ethanol extract of *A. praemorsa* leaves using MTT assay. The extract exhibited cytotoxic effect against A549 cell line dose dependently with IC_{50} value of 14.63 µg/ml.

14.3.2.2 Anti-Inflammatory Activity

Bhattacharya et al. (2009) evaluated the ethanolic and aqueous extracts of whole plant of *A. praemorsa* for its anti-inflammatory activity by Carrageenan-induced paw edema in rats. Aqueous extract exhibits the significant anti-inflammatory activity.

14.3.2.3 Antibacterial Activity

Jhansi and Khasim (2018) evaluated the antimicrobial activity of leaf extracts of *A. praemorsa* against kanamycin resistant *E. coli* by disk diffusion assay. Among various extracts employed, EA extract is more effective in displaying the marked antibacterial activity with a zone of inhibition 13 mm followed by methanol extract with 9 mm. Hoque et al. (2015) studied the antibacterial potential of this herb using the disk diffusion method. They observed that ethanol extract is more effective than other extracts in inhibiting the bacterium, *Staphylococcus aureus*.

14.3.2.4 Antifungal Potentiality

Swamy et al. (2014) evaluated the antifungal potential of *A. praemorsa*. Petroleum ether (PE) extract of leaf and root, and methanol leaf extract showed dose-dependent inhibition of *Aspergillus niger* and *Candida albicans*. However, methanol extract was ineffective in responding inhibition of above fungi. Aqueous extract from this plant was effective in causing inhibition of phytopathogenic fungi such as *Alternaria alternata*, *Curvularia lunata*, *Colletotrichum chorchori*, *Fusarium equiseti*, *Macrophomina phaseolina* and *Botryodiplodia theobromae*; further highest and least inhibitory activity was found against *C. lunata* and *M. phaseolina*, respectively (Hoque et al., 2015). Akarsh et al. (2016) investigated the antifungal activity of cow urine extract of *A. praemorsa* against some fungi; it was more effective against *Colletotrichum capsici* with 50% inhibition than *Fusarium oxysporum* with least inhibition of 11.90% only.

14.3.2.5 Antioxidant Activity

Suja and Williams (2016) screened the antiradical activity of aqueous and ethanol extracts of *A. praemorsa* by hydroxyl and DPPH radical scavenging activity. A dose-dependent scavenging of radicals was observed.

KEYWORDS

- ***Acampe ochracea***
- ***Acampe praemorsa***
- **antimicrobial efficacy**
- **antioxidant activity**
- ***Gastrochilus ochraceus***
- **petroleum ether**
- **phytochemicals**

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CHAPTER 15

Phytochemical and Therapeutic Potential of *Aerides odorata* Lour. (Orchidaceae): An Overview

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15.1 INTRODUCTION

Aerides odorata Lour. is an epiphyte, growing up to 2 m in height. Stem is profusely branched. Leaves are flat, broad, oblong, to 25 cm long and 4 cm broad, leathery, yellowish green, unequally bilobed at the tip. Inflorescence is pendulous, many-flowered, and cylindrical. Flowers are 4–5 cm long, very fragrant, waxy white, with shade of purple. *Aerides odorata* is distributed in India, Bangladesh, Burma, Indochina, China, Malaya, and Thailand.

15.1.1 ETHNOMEDICINAL USES

Root paste is taken orally twice a day with a cup of water for one month to reduce joint pain and swellings (Hossain, 2009). Leaf juice is used to treat wounds (Huda et al., 2006), healing boils, nose, and ear diseases (Hossain, 2009; Kaushik, 2013). The leaf juice is also used in the treatment of tuberculosis (Dash et al., 2008), pneumonia, dyspepsia, epilepsy, paralysis, and fracture (Akhter et al., 2017). Mashed fruit is used in healing wounds (Kaushik, 2013). Whole plant is used in the treatment of inflammation, waist ache (Akhter et al., 2017) and for digestive disorders (Rahamtulla et al., 2020). In Vietnam, herbalists believe that, if seeds are sprinkled on

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lesions, it helps in healing boils and other problems (Lawler, 1984). In Nepal, a poultice made from leaves has been used to heal wounds and cuts (Pant and Raskoti, 2013).

15.2 PHYTOCHEMICALS

Secondary metabolites such as alkaloids, coumarins, flavonoids, glycosides, phenols, steroids, and terpenoids are observed in hexane, ethyl acetate (EA) and methanol extract of leaves in *A. odorata* (Jhansi et al., 2019).

GCMS analysis of *A. odorata* EA extract displayed compounds such as 1,3-Propanediol, 1-acetate, Butanamide, β-Selinene, Longipinocarvone, and Squalene. Further, methanol extract showed compounds such as 2-Propen-1-ol, cis-11-Eicosenoic acid, Ethyl α-D-glucopyranoside, Erucic acid (Jhansi et al., 2019).

The GC-MS data of EA extract of *A. odorata* showed various compounds in typical gas chromatogram. Their peak area percentage, retention time and molecular mass were shown in Table 15.1. The major ones were Hexadecan-l-ol and 1,3-propanediol. In case of methanol extract also various compounds were recorded in typical gas chromatogram. Their peak area percentage, retention time and molecular mass were shown in Table 15.2. Among them, the major compounds were 5-Ethyl-2-methyl-2,3-dihydrofuran and (2E,6E)-3,7,11-trimethyldodeca-2,6, 10-trien-1-ol. A total of 29 compounds reported from *A. odorata*.

15.3 PHARMACOLOGICAL ACTIVITIES

15.3.1 ANTICANCER ACTIVITY

Jhansi et al. (2019) carried out an MTT assay for cytotoxicity of EA and methanol extracts of *A. odorata* at different concentrations on two different cell lines MCF-7 and HeLa. Their results revealed that the methanol leaf extract of *A. odorata* showed significant cytotoxicity effect on MCF-7 cell lines. The EA extract of the *A. odorata* at the concentration 100 µg/mL showed growth inhibition 61.128% on MCF-7 cell lines as compared to the methanol extract having 60.69%. The recorded IC_{50} value for methanol extract was 26.211 µg/mL and 41.094 µg/mL in EA extracts.

TABLE 15.1 Chemical Compounds Recorded from Ethyl Acetate Extract of *A. odorata*

Sl. No.	Name of the Compound	Peak Area (%)	R.T (min)	Mol. Mass (gms/mol)
1.	2-Methyl-5-(1,2,2-trimethycyclopentyl) phenol	0.56	4.0167	218.34
2.	1,3-Propanediol	7.00	4.5167	76.095
3.	1,2,3-Propanetriol, 1-acetate	1.74	5.8000	134.131
4.	Butanamide	6.58	6.1167	87.122
5.	Phenyl(piperidin-3-yl)methanone	4.76	9.2667	189.258
6.	4-Methyl-2-pentadecyl-1,3-dioxane	0.64	16.6500	312.538
7.	3,7,11,15-tetramethyl-2-hexadecen-1-ol	2.72	19.9900	296.539
8.	β-Selinene	6.93	20.0333	204.357
9.	Longipinocarvone	2.03	22.9833	218.34
10.	(E)-5-Methylundec-4-ene	1.69	31.2167	168.324
11.	Methyl heptadecanoate	2.80	41.4167	284.484
12.	Hexadecan-1-ol	14.72	41.5003	242.447
13.	Methyl 14-methylpentadecanoate	4.63	47.9833	270.457
14.	2-O-(2-Ethylhexyl) 1-O-pentadecyl oxalate	1.55	50.0607	412.655
15.	Squalene	2.15	58.2667	410.73

TABLE 15.2 Chemical Compounds Recorded from Methanol Extract of *A. odorata*

Sl. No.	Name of the Compound	Peak Area (%)	R.T (min)	Mol. Mass (gms/mol)
1.	2-Naphthalenemethanol, 1,2,3,4,4a,5,6,7-octahydro-α,α,4a,8-tetramethyl-, (2R-cis)-	1.15	6.9167	222.36
2.	2-Propen-1-ol, 3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-	2.41	8.1500	180.28
3.	m-Toluylaldehyde	2.30	12.6667	270.45
4.	Methyl (2E) – 3-phenyl – 2-propeonate	1.21	15.4833	163.19
5.	1,2,3-Propanetriol, diacetate	4.44	22.6667	176.17
6.	5-Ethyl-2-methyl-2,3-dihydrofuran	17.11	29.8000	112.17
7.	Ethyl α-D-glucopyranoside	4.77	34.8833	208.20
8.	6-Isopropyl-3-methyl-1-cyclohex-2-enone	4.10	35.3137	152.23
9.	3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol	6.45	38.7500	222.37
10.	Erucic acid	6.53	40.4167	338.58
11.	Linoleoyl chloride	2.48	43.1500	298.89
12.	(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol	12.32	43.4833	222.37
13.	9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)	4.47	55.9667	292.45
14.	Cis-11-Eicosenoic acid	4.17	31.4833	310.522

15.3.2 ANTIMICROBIAL ACTIVITY

Water extract of *A. odorata* showed 0.5 cm, 0.7 cm and 0.5 cm inhibition zone against antibiotic susceptible *E. coli*, ampicillin resistant *E. coli* and kanamycin resistant *E. coli*, respectively (Paul et al., 2013).

15.4 FUTURE PERSPECTIVES

It is evident from the existing literature that very little work has been done on phytochemicals in *A. odorata*. There is a need to carry out research to isolate and purify the compounds that are useful in treating various cancer diseases. In our study based on MTT assay, both the EA and methanol extracts showed profound cytotoxic activity against the cancer cell lines. Further studies on animal models are essential to confirm the anticancer efficacy of this plant.

KEYWORDS

- ***Aerides odorata***
- **anticancer activity**
- ***Escherichia coli***
- **ethnomedicinal**
- **growth inhibition**
- **pharmacological activities**
- **phytochemicals**

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CHAPTER 16

The Mexican Poppy: *Argemone mexicana* L. Bioactives and Biological Activities

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16.1 INTRODUCTION

Argemone mexicana L., commonly known as 'Mexican Poppy' or Ghamoya in Hindi, is a flowering plant belonging to the family Papaveraceae. It is a latex-containing herbaceous plant growing in tropical and sub-tropical regions of the world, found in and around agricultural and wastelands in India and Bangladesh as a common weed. It is considered an important medicinal plant in India due to the yellow juice which is exuded when the plant is cut, being used in traditional medicine to treat dropsy, jaundice, ophthalmic, scabies, and cutaneous infections. The plant is a prickly erect herb of about 1 m high with 5–10 cm long leaves which are more or less blotched with green and white patches, has a glaucous broad base, prominently pinnate lobed and spiny. The flowers are terminal, yellow, and scentless. The capsules are shiny, obovate, and the seeds are spherical, black, and pitted (Brahmachari et al., 2013).

16.2 BIOACTIVES

The phytochemical analysis of *A. mexicana* leaves extracts reveal that alkaloids, anthraquinones, flavanoids, saponins, and steroids were present in the n-hexane, ethyl acetate (EA) and methanol extracts in varying quantities (Apu, 2012). Aerial parts of *A. mexicana* include alkaloids

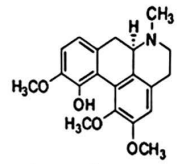
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like reticuline, protomexicine, 13-oxoprotopine, argenaxine, higenamine, 8-methoxy dihydrosanguiranine. Whole plant extracts also show presence of alkaloids like coptisine, cryptopine, muramine, argemexicaine A and B, stylopine, nor-sanguinarine, chelerythrine, oxyhydrastinine, thalifoline, tetrahydroberberine, oxyberberine, arnottianamide, angoline, 8-acetonyl dihydrosanguiranine. The seeds are said to contain berberine, protopine, sanguinarine, dihydrosanguinarine, and dihydropalmatine hydroxide (Brahmachari et al., 2013). Sanguinarine is restricted to the roots and mature seeds. Other alkaloids found were cheilantifoline, dihydrocheleritrine, nor-cheleritrine, dihydrosanguinarine, nor-sanguinarine, hydroxymethylstylopine, 6-acetonylsanguinarine, oxyhydrastine, and isocoridine. In addition, N-demethyloxysanguinarine, pancorine, (+)-argenaxine, as well as argemexicaines A and B, have also been found in this plant (Rubio-Pina et al., 2013).

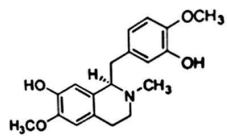
Two benzophenanthridine-type alkaloids, N-demethyloxysanguinarine, and pancorine; three benzylisoquinoline-type alkaloids, (+)-1,2,3,4-tetrahydro-1-(2-hydroxymethyl-3,4-dimethoxyphenylmethyl)-6,7-methylenedioxyisoquinoline, (+)-higenamine and (+)-reticuline have been isolated from the chloroform extract of aerial parts of *A. mexicana* (Chang et al., 2003a). A benzylisoquinoline alkaloid, argemexirine, together with two known protoberberine alkaloids, dl-tetrahydrocoptisine, and dihydrocoptisine, have been isolated from the methanolic extract of the whole plant of *A. mexicana*. (Singh et al., 2010a). Four quaternary isoquinoline alkaloids, dehydrocorydalmine, jatrorrhizine, columbamine, and oxyberberine, have been isolated from the whole plant of *A. mexicana* (Singh et al., 2010b).

Plant resins like argemonine are also found in *A. mexicana*. The oils consist of argemonic acid, myristic acid, palmitic, and stearic acid; arachidic, oleic, linoleic, mexicanic acid. The plant also contains terpenoid transphytol, β-amyrin and steroid stigma-4-en-3, 6-dione. The roots are found to contain β-sitosterol. Carbohydrates found in *A. mexicana* include lactose and arabinose. Long chain alcohols like triacotan-11-ol, triacotan-6, 11,-diol and mexicanic acid are also found in the aerial parts (Brahmachari et al., 2013).

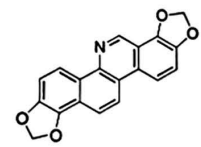
Quercetin, quercetrin, mexitine, and rutin are the flavonoids present throughout the whole plant. It also contains phenolics and aromatic acids like 5,7-dihydroxy chromone-7-neohesperidoside, tannic acids, caffeic acid, ferulic acid, benzoic acid, cinnamic acid and vanillic acid. Flavonoids like luteolin and eriodictyol have been isolated from the seeds and isorhamnetin from the flowers of *A. mexicana*. α-tocopherol, adenosine, and adenine have been isolated from the aerial parts of *A. mexicana* (Brahmachari et al., 2013).



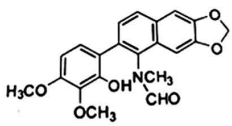
Isocorydine



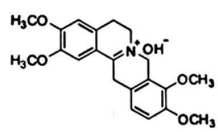
Reticuline



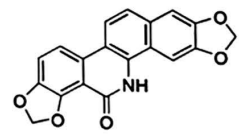
Nor-sanguinarine



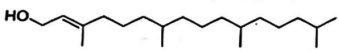
Arnottianamide



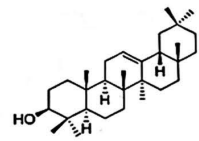
Dihydropalmatine hydroxide



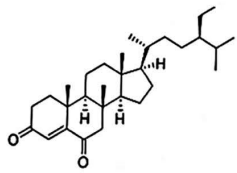
N-demethyloxysanguinarine



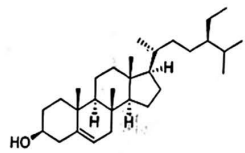
Trans-phytol



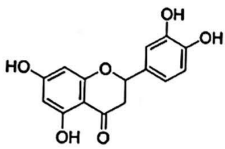
Beta amyrin



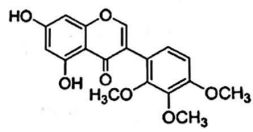
Stigma-4-en-3,6-dione



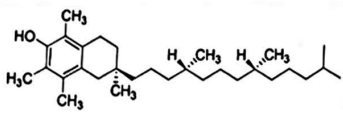
Beta sitosterol



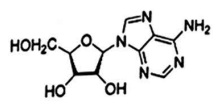
Eriodictyol



Mexitin



Alpha tocopherol



Adenosine

16.3 PHARMACOLOGY

16.3.1 ANTI-MICROBIAL ACTIVITY

The antimicrobial activity of the extracts of *A. mexicana* leaves tested against Gram positive, Gram negative bacteria and *Candida* species did not show significant inhibition of growth. The extracts were found to be partially effective (zone of inhibition between 9 mm and 12 mm) at the higher doses (Smania, 1995). Crude stem extracts were effective against a number of food-borne Gram positive and Gram negative bacteria and exhibited zones of inhibition in the range of 10.1 to 21.4 mm at the concentration of 10 µl (Rahman et al., 2009). Various leaves extract were found to exhibit anti-pseudomonal activity against multi-drug resistant *P. aeruginosa* isolated from clinical samples (Sahu et al., 2012). Alkaloids like dehyrocorydalmine and oxyberberine isolated from *A. mexicana* showed anti-fungal activity against fungal strains such as *Helminthosporium* sp., *Curvularia* sp., *Fusarium udum*, etc. (Singh et al., 2009). *A. mexicana* seed extract was found to exhibit toxicity against a number of fungal strains. The latex from the plant shows toxicity against *Trichophytan mentagrophytes* (Brahmachari et al., 2013). The leaf extract was found to be toxic to fruit pathogens like *Alternaria alternata, Dreschlera halodes* and *Helminthosporium speciferum* (Srivastava and Srivastava, 1998). Methanolic extracts of the stems and leaves of *A. mexicana* showed anti-microbial activity against *T. vaginalis* growth by inhibiting trophozoite growth, and there was a clear dose-dependent response as the percentage of inhibition increased with increasing concentration of extract. The IC_{50} values of both the extracts against *T. vaginalis*, estimated via the Probit method, were less than 100 µg/ml. (Elizondo-Luevano et al., 2020). About 1 mg of *A. mexicana* extract from either the seed, leaf, inner root or outer root using methanol and hexane were tested using disc diffusion method against *Staphylococcus aureus, Bacillus cereus, Escherichia coli, Proteus mirabilis, Candida albicans* and *Saccharomyces cerevisiae.* Outer root extract in methanol showed promising results against *Staphylococcus aureus, Bacillus cereus, Escherichia coli* and *Saccharomyces cerevisiae.* (Orozco-Nunnelly et al., 2021).

16.3.2 ANTIOXIDANT ACTIVITY

EA and methanol extracts showed higher free radicals scavenging ability (on the basis of median inhibitory concentration, IC_{50} of DPPH, NO free radicals) compared to the n-hexane extracts. It was observed that there was a

pattern of the antioxidant properties exhibited by extracts of *A. mexicana* in DPPH and NO assays (Apu, 2012).

16.3.3 TOXICITY STUDY

n-hexane, EA, and methanol extracts of *A. mexicana* leaves did not show any apparent *in-vitro* toxicity compared to positive control as the extracts showed higher LC_{50} values than 100 µg/ml (Apu, 2012). Cytotoxicity of the crude extract of *A. mexicana* stem and leaf was carried out via a human erythrocyte hemolysis test. It was found that none of the extracts were significantly cytotoxic at even the highest concentration of 1,000 µg/ml. (Elizondo-Luevano et al., 2020).

16.3.4 LARVICIDAL ACTIVITY

Acetone fraction of petroleum ether (PE) extract of *A. mexicana* seeds showed significant larvicidal and growth inhibiting activity against the 2nd instar larvae of *Aedes aegyptii* at concentrations ranging from 25 to 200 ppm at both laboratory and field conditions (Sakthivadivel and Thilagavathy, 2003). PE extract of the leaves also showed high larvicidal potential against 3rd–4th instar larvae of *Culex quinquefasciatus* (Sakthivadivel et al., 2012).

16.3.5 ANTI-HELMINTHIC ACTIVITY

Aqueous extract of *A. mexicana* also exhibited significant anti-helminthic activity against the Indian earthworm *Pheretima posthuma* (Jaliwala et al., 2011).

16.3.6 MOLLUCICIDAL ACTIVITY

Alkaloids like protopine and sanguinarine isolated from *A. mexicana* exhibited mollucicidal activity in *Lymnaea acuminata* by significantly reducing the protein, free amino acids, DNA, and RNA levels in the nervous tissue. It also showed a decrease in the phospholipids level and a simultaneous increase in the rate of lipid peroxidation (LPO) in the tissue (Singh and Singh, 1999).

16.3.7 INSECTICIDAL/PESTICIDAL ACTIVITY

Aqueous leaf extract of *A. mexicana* exhibited lousicidal activity on *Lipeurus tropicalis* Peters by conducting mortality and repellancy tests (Kumar et al., 2002). PE and aqueous extract of *A. mexicana* leaves exhibited significant anti-feedant activity against 2nd stage *Henosephilachna vigintiocto punctata* larvae (Rao et al., 1990). Oil extracted from *A. mexicana* seeds is found to kill *Meloiodogyne incognita* larvae. Nematode infection in terms of root galling, root protein content and nematode population in soil and roots reduced after application of aqueous mixture to soil and leaves of *Hibiscus esculentus* inoculated with *M. incognita* (Das and Sukul, 1998).

16.3.8 ANTI-PARASITIC ACTIVITY

Aqueous extract of aerial parts of *A. mexicana* exhibited anti-parasite activity against the chloroquine resistant K1 strain of *Plasmodium falciparum* in a randomized controlled clinical trial (Schrader et al., 2012). Methanolic extract of *A. mexicana* and its main component berberine inhibit the viability of *Schistosomes mansoni* in the adult stage and the effects of both were time and dose-dependent. The highest efficacy was observed in berberine at a concentration of 5 μM during an incubation period of 72 h, and from 10 μM at 24 h with effect in both sexes, combined to the separation of the couples. The effect was much more pronounced against the male. Schistosomes exposed to both treatments were found to exhibit mobility changes with atypical muscle contractions that became slower over time when treatment concentration increased and even parasite death was observed (Elizondo-Luévano et al., 2021).

16.3.9 ANTI-INFLAMMATORY ACTIVITY

Ethanolic extract of *A. mexicana* leaves showed significant anti-inflammatory and analgesic effect in mice (Sharma et al., 2010). The leaves extract also showed similar effects in rats (Sukumar et al., 1984).

16.3.10 CLOT LYSIS ACTIVITY

N-hexane and ethanolic extracts of *A. mexicana* showed statistically highly significant clot lysis activity compared to negative control (Apu, 2012).

16.3.11 WOUND HEALING ACTIVITY

Methanolic extract of *A. mexicana* leaves was found to accelerate wound healing in Wistar albino rats using excision, incision, and dead space wound models (Dash et al., 2011).

16.3.12 ANTI-STRESS AND ANTI-ALLERGIC ACTIVITY

Aqueous and methanolic extracts of *A. mexicana* stems were tested to exert anti-allergic as well as anti-stress effect in asthma developed by milk-induced leucocytosis and milk-induced eosinophilia in Albino mice model. The extracts exhibited a significant decrease in both leuococytes and eosinophils in-vivo (Bhalke and Gosavi, 2009).

16.3.13 VASO-CONSTRICTOR AND VASO-RELAXANT EFFECTS

Methanolic extract of aerial parts of *A. mexicana* was found to produce relaxation from contraction induced by norepinephrine in a concentration dependent manner in the rat aortic rings. It was observed that the extract was able to induce a direct and dual specific effect upon the vascular smooth muscle, mediated, at least in parts by adrenergic receptors (Paez-sanchez et al., 2006).

16.3.14 CYTOTOXIC/ANTI-CANCER ACTIVITY

Methanolic extract of *A. mexicana* leaves exhibited cytotoxic activity against healthy mouse fibroblasts (NIH3T3) and three human cancer cell lines (AGS, HT-29, MDA-MB-135S) using MTT assay (Uddin et al., 2011). Ethanolic extract of *A. mexicana* was reported to exhibit inhibitory effect against human cancer cell lines such as HeLa-B75 (48%), HL-60 (20.15%) and PN-15 (58.11%) (Gacche et al., 2011). Methanolic extract of *A. mexicana* leaves also showed anti-cancer activity against HeLa and MCF-7 cancer cell lines based on MTT assay results (Gali et al., 2011). Some isolated alkaloids from *A. mexicana* like chelerythrine, angoline, and argenaxine were evaluated for their cytotoxicity to human nasopharyngeal carcinoma (HONE-1) and human gastric cancer (NUGC) cell lines. Chelerythrine was found to exhibit significant activity against NUGC cell line and angoline inhibited both

types. (+)-Argenaxine showed moderate activity against the NUGC cell line (Chang et al., 2003a). *A. mexicana* extracts were tested against T84 human colon cancer cells and it was found that the outer root methanol and seed hexane extracts have the greatest inhibitory activity. Cells treated with inner and outer root hexane extracts survived better than cells that were treated with hexane alone, with mean viability percentages greater than 100% after being normalized to the control (solvent alone). This shows that compounds like chelerythrine and berberine in these extracts could be promoting cell growth. Treatment with the root methanol extract, the unexplored RKO colon cancer cells were found to downregulate the c-MYC oncogene and upregulate the tumor suppressor APC gene (Orozco-Nunnelly et al., 2021). A study on the effect of alkaloids like 13-oxoprotopine, protomexicine, 8-methoxydihydrosanguinarine, dehydrocorydalmine, jatrorrhizine, and 8-oxyberberine on SW480 human colon cancer cell line showed that these alkaloids strongly inhibit the cell proliferation in human colon cancer cells at varying concentrations by MTS assay (Singh et al., 2016).

16.3.15 ANTI-FERTILITY ACTIVITY

Three isoquinoline alkaloids, dihydropalmatine hydroxide, berberine, and protopine isolated from *A. mexicana* seeds exhibited anti-fertility activity in male dogs. Significant reduction in a number of spermatids and total number of mature leydig cells were observed (Gupta et al., 1990).

16.3.16 EFFECT ON ILEUM ORGAN

Methanolic extract of *A. mexicana*, with its partially purified fraction and isolated pure compounds like protopine and allocrytopine were observed to reduce the morphine withdrawal effect in Guinea pig isolated ileum in a concentration dependent manner. This suggests the possible use of isoquinoline alkalolids as potential treatment agents for drug abuse (Capasso et al., 1997).

16.3.17 ANTI-DIABETIC ACTIVITY

Aqueous extract of *A. mexicana* at a dose of 200 and 400 mg/kg body weight was found to have a hypoglycemic effect in alloxan induced diabetic

rats. Significant reduction in blood glucose levels, plasma urea, creatinine, triacylgyleride, cholesterol levels were observed in treated rats compared to diabetic control rats (Nayak et al., 2011).

16.3.18 ANTI-HEPATOTOXIC ACTIVITY

Aqueous extract of *A. mexicana* stems in CCl_4 induced hepatotoxic male rats showed significant anti-hepatotoxic effect on oral administration of 150 and 250 mg/kg body weight. Reduction in the levels of serum aspartate transaminase, alanine aminotransferase and alkaline phosphatase (ALP) was observed (Das et al., 2009).

16.3.19 ANTI-HIV ACTIVITY

Alkaloid Benzo(c) phenanthridine isolated from methanolic extract of whole plants of *A. mexicana* exhibited potent anti-HIV activity in H9 lymphocyte assay (Chang et al., 2003b).

16.3.20 NEUROLOGICAL EFFECTS

Berberine, found commonly in *A. mexicana* leaves, produces muscle spasms and convulsions caused by its inhibitory action on acetylcholinesterase (AChE). Berberine can also modulate neurotransmitter-receptor systems in the brain, and it could be utilized in the treatment of neurodegenerative and neuropsychiatric disorders. Clinical trials showed that berberine can pass across the blood-brain barrier, reaching the hippocampus and exerting its effects directly on these cells. This alkaloid is also said to inhibit the activity of monoamine oxidase A and B (MAO-A and MAO-B), which are associated with Alzheimer's disease and other neurodegenerative disorders. Berberine is also found to reduce the aggregation of amyloid peptide (A), a component of the amyloid plaque linked to Alzheimer's (Rubio-Pina et al., 2013).

KEYWORDS

- ***Alzheimer's disease***
- ***Argemone mexicana***
- **human gastric cancer**
- **human nasopharyngeal carcinoma**
- **Mexican poppy**
- **neurological effects**

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CHAPTER 17

Ethnobotanical Uses, Phytochemistry, and Pharmacological Activities of *Cryptolepis dubia* (Burm.f.) M. R. Almeida

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17.1 INTRODUCTION

Cryptolepis dubia (Burm.f.) M. R. Almeida belongs to the family Apocynaceae. Synonyms of this species include *Cryptolepis buchanani* R. Br. *ex* Roem. & Schult.; *Cryptolepis reticulata* Wall.; *Nerium reticulatum* Roxb. Indian Sarsaparilla, Milk weed, Krishna Sariva, Karanta, Shyamalata, Karibanta, and Gopikonioro are some of the common names of the plant (Parrotta, 2001).

Branches glabrous, terete. Leaves elliptic-oblong or oblong-lanceolate, base acute, apex acute or shortly acuminate and mucronate, margins entire, shining green above, pale or glaucous beneath, glabrous. Flowers greenish-yellow, in short, axillary, paniculate cymes. Calyx glabrous; tube very short. Corolla tube 2 mm long. Stamens 5. Corona 5, fleshy, oblong-spathulate scales, inserted near mouth of corolla tube. Follicles 5–10 cm long, paired, lanceolate, cylindric, ridged, tapering to a blunt point. Seeds many. The plant is native to Sri Lanka, Thailand, Andaman Island, Bangladesh, China

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South-Central, Assam, China Southeast, East Himalaya, West Himalaya, Vietnam, Myanmar, Nepal, Bhutan, Pakistan, Laos, and India (POWO, 2019).

In traditional Ayurvedic medicinal practice, the root of the plant is used as a substitute for *Hemidesmus indicus* (L.) R. Br. ex Schult. and used in the treatment of gout, wounds, polyuria, anemia, and jaundice. The filtered extract from the powdered roots is taken internally to relieve stomach pain in northern Andhra Pradesh (Parrotta, 2001). The plant is traditionally used as medicine against skin diseases, diarrhea, bone fracture, loss of appetite, fever, and rickets in children (Panja et al., 2020). In Thailand, the plant is reported to cure pain-related disorders such as stiffness of tendons, muscle tension, and arthritis. Leaves are used to tie around the inflamed area to treat myalgia and arthritis (Hanprasertpong et al., 2014).

17.2 BIOACTIVES

Dutta et al. (1978, 1980) isolated new nicotinoyl glucoside compounds such as buchananine (6-O-nicotinoyl-α-D-glucopyranose) and 1,3,6-O-trinicotinoyl-α-D-glucopyranose (CB-2) from *Cryprolepsis dubia* (Syn,: *C. buchanani*) stem. Khare and Shah (1983) have also reported the compound buchananine from the leaves of the plant. Further, Venkateswara et al. (1987, 1989) have isolated a digoxin-type new steroidal glycoside compound called 'cryptosin' from *in vitro* grown biomass and leaves of *C. buchanani*.

Purushothaman et al. (1988) reported the major cardenolide glycoside compounds such as cryptanoside A and -C from the leaves and roots of *C. dubia* (=*C. buchanani*), respectively. The compounds were further characterized as sarverogenin 3-*O*-*α*-L-oleandroside and sarverogenin 3-*O*-[*β*-D-glucopyranosyl-(1→4)-*α*-L-oleandroside] based on their ^{1}H, ^{13}C NMR spectra and chemical correlation with sarverogenin. Authors have also reported one of the principal constituents of the root extract called germanicoldocosanoate. However, the minor constituent cryptanoside B was isolated from the leaf extract and the compound cryptanoside D was isolated from acetylation of cryptanoside C (Purushothaman et al., 1988). Further, Pande et al. (2006) have isolated a novel serine protease enzyme named cryptolepain from the latex of the plant.

The ethanolic leaf extract of the plant was carried out for GC-MS analysis and total 20 compounds were reported by Padmalochana et al. (2013). Among all the compounds, tetradecanoic acid (15.69%), n-hexadecanoic acid (11.44%), oleic acid (7.70%), and octadecanoic acid (1.89%) reported with higher peak area percentage composition (Figure 17.1).

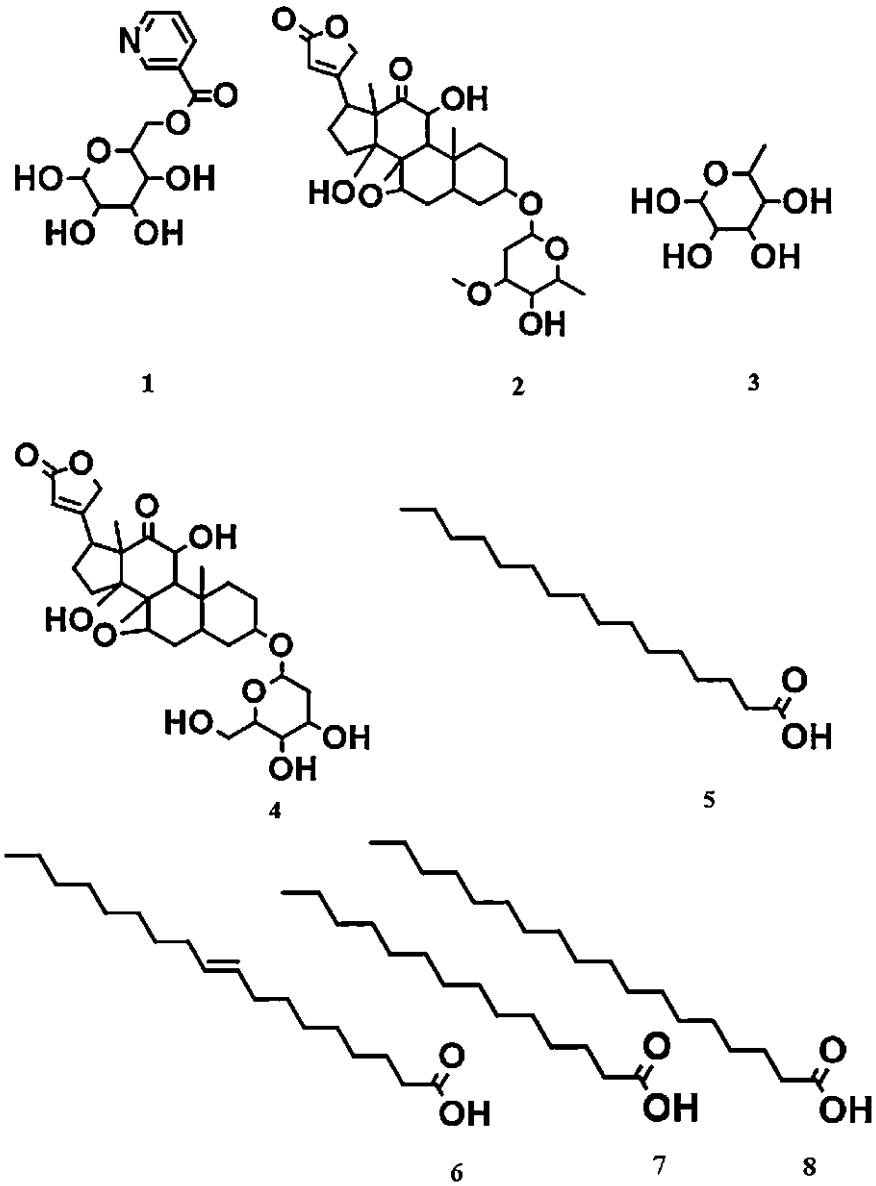


FIGURE 17.1 Structures of buchananine (1); cryptanoside A (2); α-D-fucose (3); cryptosin (4); n-hexadecanoic acid (5); oleic acid (6); tetradecanoic acid (7); and octadecanoic acid (8).

17.3 PHARMACOLOGY

17.3.1 INSECTICIDAL ACTIVITY

Ashwini et al. (2010) performed the insecticidal property of chloroform, acetone, and methanolic leaf extracts of *C. dubia* (*C. buchanani*) against *Aedes aegypti* second instars larvae. The extracts revealed dose dependent mortality of the tested larvae. It was evident from the results that chloroform and methanol extracts found more efficient with 100% larval mortality at 15 mg/mL concentration. The extracts at 5 mg/mL concentration displayed more than 50% mortality of larvae**.**

17.3.2 ANTIMICROBIAL ACTIVITY

Sittiwet and Puangpronpitag (2009) carried out the antibacterial activity of aqueous leaf extract of *C. dubia* against several food pathogens. It was reported that the aqueous extract at 500 g/L concentration showed good inhibitory effect against *Lactobacillus plantarum* (23.0 ± 1.3 g/L), *Escherichia coli* (21.0 ± 0.6 g/L), *Klebsiella pneumoniae* (19.6 ± 0.7 g/L). The extract against all the tested strains showed minimum inhibition concentration (MIC) and minimum bactericidal concentration (MBC) in the range of 1 to 16 and 2 to 32 g/L, respectively. Bholay et al. (2016) explored antimicrobial efficacy of acetone, EA, ethanol, and methanol extracts of leaves using agar well diffusion method against several strains such as *Aspergillus niger*, *Bacillus subtilis*, *Candida albicans*, *Citrobacter diversus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Staphylococcus aureus*, *Vibrio cholerae* and *Xanthomonas citri*. Results from the study indicated that EA extract contributed maximum growth inhibition against *X. citri* (27.6 ± 0.3 mm) followed by *P. vulgaris* (27.5 ± 1.0 mm), *V. cholerae* (26.5 ± 0.5 mm), *K. pneumoniae* (25.3 ± 1.0 mm) and *S. aureus* (22.8 ± 1.0 mm).

The antifungal activity of methanol and aqueous leaf extracts of the plant against human dermatophytic fungi such as *Microsporum gypseum* (MTCC 2819), *Chrysosporium keratinophilum* (MTCC 1367), *Chrysosporium indicum* (MTCC 4965) and *Trichophyton rubrum* (MTCC 3272) was studied through agar well diffusion method (Vinayaka et al., 2010). Methanol and aqueous extracts found more potent against *T. rubrum* and *C. keratinophilum* with higher inhibition zones (14 mm each). Similarly, the strains *M. gypsium* and *T. rubrum* found sensitive against water extract with 12 mm zone of inhibition, respectively. Whereas, the standard amphotericin B showed the greatest inhibition zones against all the strains with 19, 20, and 21 mm, respectively.

17.3.3 ANTI-INFLAMMATORY ACTIVITY

Laupattarakasem et al. (2006) performed anti-inflammatory activity of aqueous and alcoholic extracts of different parts of *Acanthus ebracteatus*, *Oroxylum indicum*, *Cryptolepis dubia* (*C. buchanani*) and *Derris scandens* using different *in vitro* and *in vivo* methods relevant to anti-inflammatory activity. Among all, the ethanol extract of *C. buchanani* stem showed weaker eicosanoid synthesis inhibition with 31% at 500 µg/mL concentration. However, both the extracts of *C. buchanani* stem failed to produce myeloperoxidase (MPO) release in the cells and to cause *in vivo* effect on induced edema in rats. In contrast to this study, Laupattarakasem et al. (2006) found the potential anti-inflammatory activity of 50% ethanol extract, which caused reduction in inflammation of carrageenan-induced rat paw edema (0.47 ± 0.06 mL paw volume after 3 hours of induction). In addition, the rat peritoneal leukocytes stimulated from calcium ionophore A23187 showed a significant reduction in the formation of eicosanoid at 800 µg/mL concentration. However, the extract proposed significant reduction in the formation of granulation tissue and it significantly inhibited TNF-α production (52.19%) at 100 µg/mL dose in comparison to the standard dexamethasone (60.17%; dose 1 µM). Further, Hanprasertpong et al. (2014) reported anti-inflammatory activity of methanolic stem extract in ethyl phenylpropiolate (EPP) induced ear edema in male Spraque-Dawley rats. Both the extracts and standard indomethacin at 1 mg/ear dose significantly affected ear edema (63 ± 10.23 and 65 ± 4.28 mm at 120 minutes, respectively). Similarly, in carrageenan-induced paw edema, the percent reduction of paw edema in extract and standard indomethacin was 46.06 and 58.36% at 500 mg/kg and 10 mg/kg doses. Further, in acetic acid-induced writhing responses the extract showed significant reduction of the number of writhes significantly at 125 and 250 mg/kg dose.

Sriset et al. (2017) revealed anti-inflammatory potentiality of ethanol extract of stem at 1, 5, 50, and 100 µg/mL doses by inhibiting the TNF-α production in lipopolysaccharide-stimulated (LPS) human leukemia (HL) monocytic THP-1 cell. Wanikiat et al. (2019) carried out *in vitro* anti-inflammatory activity of methanol extract of stem against human neutrophil functional responsiveness model. In fMLP-induced neutrophil chemotaxis, the extract significantly suppressed in a concentration-dependent manner (0.1–100 µg/mL) with IC_{50} of 140.4 ± 18.2 µg/mL compared to the standard indomethacin (IC_{50} 17.7 ± 2.5 µg/mL). In fMLP induced MPO production assay, the extract significantly inhibited with IC_{50} of 108.3 ± 8.9 µg/mL

compared to standard indomethacin (IC_{50} 43.7 ± 3.6 μg/mL). Similarly, in fMLP-induced elastase release, the extract found effective with IC_{50} > 7,000 μg/mL, in contrast to indomethacin (IC_{50} 52.3 ± 6.5 μg/mL).

17.3.4 IMMUNOMODULATORY ACTIVITY

Kaul et al. (2003) investigated the immunomodulatory activity of ethanol extract (95%) of root in rat and mice models. The extract at 12.5 to 200 mg/kg oral doses showed an increase of 6.52 to 21.73% stimulation in rats. Whereas in mice, it showed a dose-related increase of 7.14 to 35.71% at 12.5 to 200 mg/kg dose. In the case of humoral antibody production, the extract produced a dose-related increase (12.5–200 mg/kg) in primary antibody synthesis. The antibody response was increased at a linear dose-dependent manner and it was observed up to 100 mg/kg. Further, it was significant at 200 mg/kg dose in both mice and rats.

17.3.5 ANTIOXIDANT ACTIVITY

Ashwini et al. (2010) studied the antioxidant activity of methanol, acetone, and chloroform extracts of leaves of *C. dubia* (*C. buchanani*) through hydroxyl, DPPH, and Fe^{3+} radical scavenging assays. Antioxidant activity of all the extracts were found to be dose-dependent and in all the antioxidant parameters, the methanol extract exhibited potent antioxidant activity with dose-dependent manner (60–75% scavenging from 0–1 mg/mL concentration).

17.3.6 ANTICANCER ACTIVITY

The anticancer activity of silver nanoparticles synthesized from *C. dubia* (*C. buchanani*) leaf extract was determined by Panja et al. (2020). The synthesized nanoparticles were more toxic to HeLa cells (91.0% cell death) at 25 μg/mL concentration with LD_{50} 3.98 μg/mL. In contrary, the nanoparticles killed 77.9% of HEK-293 populations at 25 μg/mL concentration with 9.45 μg/mL LD_{50}.

17.3.7 CHONDROPROTECTIVE ACTIVITY

Hanprasertpong et al. (2014) carried out chondroprotective effects of methanolic stem extract in cartilage explant culture. The extract at 50 μg/

mL significantly reduced the hyaluronan and sulfated glycosaminoglycan levels in culture media and it restored the collagen and uronic acid within the cartilage tissues. Whereas, the extract at 12.50, 25, 50 µg/mL significantly suppressed the matrix metalloproteinase-2 (MMP) activity.

17.3.8 ANTIPYRETIC ACTIVITY

Nishant et al. (2011) studied in-vivo antipyretic activity of ethanol and water extracts of leaves using Brewer's yeast-induced pyrexia in rats. Both ethanolic and aqueous extracts had significant dose-dependent antipyretic properties at 200 and 400 mg/kg concentration. Among these two, the aqueous extract achieved significant lowering of average rectal temperature (36.92 ± 0.10 and 38.02 ± 0.15°C, respectively) at 200 and 400 mg/kg doses after 3 hours of induction of pyrexia compared to the standard 10% v/v propylene glycol solution (38.17 ± 0.18°C).

17.3.9 HEPATOPROTECTIVE ACTIVITY

Padmalochana et al. (2013) investigated the hepatoprotective activity of the liver homogenates of Wistar albino rats administered with 250 and 500 mg/kg doses of ethanolic leaf extract. The enhancement of glutathione peroxidase, glutathione-s-transferase, superoxide dismutase, catalase (CAT), reduced glutathione (GSH), and thiobarbituric acid were significantly enhanced at 500 mg/kg dose.

KEYWORDS

- **buchananine**
- ***Cryptolepis buchanani***
- ***Cryptolepis dubia***
- **cryptosin**
- **hepatoprotective activity**
- **minimum bactericidal concentration**
- **minimum inhibition concentration**

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CHAPTER 18

White Turmeric (*Curcuma zedoaria* Rosc.): Bioactives and Pharmacological Activities

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18.1 INTRODUCTION

Curcuma zedoaria Rosc., commonly called zedoary or white turmeric, belongs to the family Zingiberaceae. It is a herb with rhizomatous stem and leaves having purple veins and is native to India, Sri Lanka and Bangladesh. The rhizomes are known as kachore in the commercial market and are used as expectorant, against asthma, acute inflammation, arthritis, etc. (Nadkarni, 1999). The roots of this plant are a rich source of Shoti starch which is often used as an alternative for arrowroot and barley. Lobo et al. (2009) reviewed the chemical, pharmacological, and ethnomedicinal properties of *C. zedoaria* rhizomes.

18.2 BIOACTIVES

C. zedoaria is found to be a rich source of essential oils (EOs), starch, curcumin, arabin, gums, etc. Several researchers have worked on *C. zedoaria* to isolate phytochemical components. More than 10 sesquiterpenes isolated and structurally characterized by Makabe et al. (2006). The sesquiterpenes isolated by them are furanodienone, furanodiene, curzerenone, curzeone, germacrone, zedorone, zedoaronediol, 13-hydroxy germacrone, dihydrocurdione, and curcumenone. Syu et al. (1998) isolated demethoxycurcumin,

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3,7-dimethylindan-5-carboxylic acid, curcolonol, and guaidiol from ethyl alcohol extract of *C. zedoaria* rhizome.

Seasonal variation of curcumenol and dihydrocurdione from various underground organs of *C. zedoaria* grown in Brazil was described by Christiane et al. (2006). This was analyzed by high resolution gas chromatography. It was observed that the amount of terpenoids was 3 times more in mother rhizomes in autumn as compared to the other parts and seasons studied. New sesquiterpenes (eudesmane type) zedoarofuran and (guaiane or secoguaiane type) 4-epicurcumenol, zedoarolides A and B neocurcumenol, gajutsulactones A and B, were isolated from aqueous acetone extract with various known compounds using ^{1}H and ^{13}C NMR spectroscopic studies and by detailed comparison with closely related compounds. Shiobara et al. (1985, 1986) isolated zedoarol, 13-hydroxygermacrone, curzeone, sesquiterpenoids curcumenone, curcumanolide-A, and curcumanolide-B. Two sesquiterpenoids α-turmerone and β-turmerone were isolated from the rhizome of *C. zedoaria* (Hong et al., 2001). Around 36 compounds isolated from EOs of *C. zedoaria*, only two compounds were characterized structurally (epicurzerenone and curzerene) by Mau et al. (2003). Eudesmane-type sesquiterpene, zedoarofuran, and six guaiane- or seco-guaiane-type sesquiterpenes, 4-epicurcumenol, neocurcumenol, gajutsulactones A and B, and zedoarolides A and B, were isolated by Matsuda et al. (2001) from aqueous acetone extract of rhizome of *C. zedoaria* together with 36 known sesquiterpenes and two diarylheptanoids.

Different techniques applied for extraction of EOs from rhizomes of *C. zedoaria* has an impact on isolation and characterization demonstrated by various researchers:

1. The essential oil obtained by hydro-distillation of *C. zedoaria* rhizomes native to North-East India (Purkayastha et al., 2006) has been analyzed by GC and gas chromatography-mass spectrometry (GC-MS). Around 37 phytoconstituents representing about 87.7% of the total essential oil have been identified and characterized. Curzerenone (22.3%) was found to be the major component, followed by 1,8-cineole (15.9%) and germacrone (9.0%) (Singh et al., 2002).
2. The presence of 1,8-cineole (18.5%), cymene (18.42%), α-phellandrene (14.9%) and β-eudesmol (10.6%) in EOs of rhizomes of *C. zedoaria* was revealed by Garg et al. (2011).
3. The essential oil of the dried *C. zedoaria* rhizome was extracted using simultaneous steam distillation (SD) and solvent extraction (SE) and its fractions were prepared by silica gel column chromatography. In total,

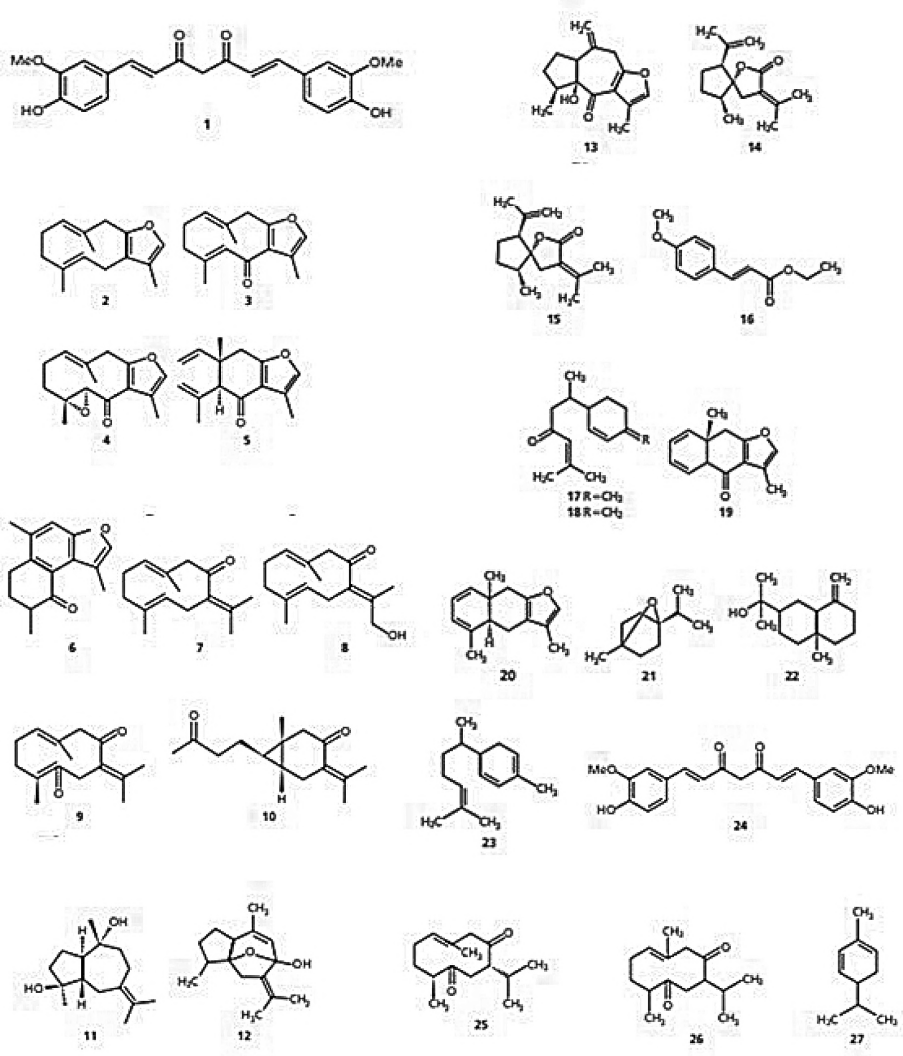


FIGURE 18.1 Structures of the biologically active compounds isolated from *C. zedoaria*. (1) Cucrumin; (2) furanodiene; (3) furanodienone; (4) zedorone; (5) curzerenone; (6) curzeone; (7) germacrone; (8) 13-hydroxygermacrone; (9) dihydrocurdione; (10) curcumenone; (11) zedoaronediol; (12) curcumenol; (13) zedoarol; (14) curcumanolide-A; (15) curcumanolide-B; (16) ethyl para-methoxycinnamate; (17) and (18) b-turmerone; (19) epicurzerenone; (20) curzerene; (21) 1,8-cineole; (22) b-eudesmol; (23) zingiberene; (24) dihydrocurcumin; (25) curdione; (26) neocurdione; and (27) a-phellandrene.

36 compounds were identified in the essential oil wherein 17 terpenes, 13 alcohols and 6 ketones were present (Hong, 2002). Epicurzerenone and curzerene were found to be in highest amounts (24.1 and 10.4%). Curcumin, dihydrocurcumin, tetrahydro-demethoxycurcumin, and tetra-tetrahydro bisdemethoxycurcumin were isolated along with two bisabolane-type sesquiterpenes from 80% aqueous acetone extract of the *C. zedoaria* rhizome (Mau et al., 2003).

Researchers have also extracted EOs from leaves of *C. zedoaria* by hydrodistillation and were analyzed by GC and GC-MS. Around 23 compounds were identified and characterized, accounting for approx. 75% of the essential oil composition. The oil of *C. zedoaria* mainly includes mono and sesquiterpenoids, monoterpene hydrocarbons (2.3%), oxygenated monoterpenes (26%), sesquiterpene hydrocarbons (38%) and oxygenated sesquiterpenes (13.5%). Leaf oil constituents are α-terpinyl acetate (8.4%), isoborneol (7%) and dehydrocurdione (9%) (Figure 18.1) (Mau et al., 2003).

18.3 PHARMACOLOGY

18.3.1 ANTIMICROBIAL AND ANTIFUNGAL ACTIVITY

Hexane, acetone, petroleum ether (PE), chloroform, and alcoholic extracts of rhizomes of *C. zedoaria* exhibited antibacterial activity against *Bacillus subtilis* NCIM 2603, *Micrococcus luteus* NCIM 2574, *Proteus mirabilis* NCIM 2300 and *Klebsiella pneumoniae* NCIM 2957 and antifungal activity against *Candida albicans* NCIM 3102 and *Aspergillus niger* NCIM 596 using agar diffusion method (Wilson et al., 2005). Essential oil obtained from *C. zedoaria* showed activity against *Corynebacterium amycolatum* (IFO 15207), *Candida albicans* (IFO 1594), *Staphylococcus aureus* (IFO 14462), *Escherichia coli* (IFO 15034) and *Aspergillus ochraceus* (IFO 31221) using Petri plate-paper disc method (Yonzon et al., 2005). Ficker et al. (2003) found *C. zedoaria* extracts to possess pronounced antifungal activity against human pathogenic fungi by disc diffusion bioassay using amphotericin B and Ketoconazole as positive control. Bugno et al. (2007) examined the antimicrobial activity of *C. zedoaria* extract against oral microflora viz *Streptococcus mutans, Enterococcus faecalis, S. aureus* and *C. albicans.* Authors have found that the antimicrobial activity of *C. zedoaria* was as effective as that of commercial products.

Ethyl p-methoxycinnamate (EPMC), the major antifungal principle phytoconstituent present in *Curcuma zedoaria*, was isolated from the methanol extract of dried rhizomes by Gupta et al. (1976). EPMC inhibited the growth various fungi including *Aspergillus niger, Epidermophyton floccosum, Trichophyton rubrum* and *Saccharomyces cerevisiae* at a concentration less than 10 μg/ml; *A. fumigatus, Fusarium oxysporum, Microsporum gypseum, Penicillium purpurogenum, Sclerotium rolifsii, Trignoposis variabilis, Geotricular candiade,* and *Helminthosporium oryzae* at a concentration less than 25 μg/ml; and *Candida krusei* and *T. mentagrophytes* at a concentration less than 50 μg/ml.

18.3.2 ANTI-AMOEBIC ACTIVITY

Ethanolic extract of rhizome of *C. zedoaria* showed inhibitory effect on the growth of *Entamoeba histolytica* at a concentration of 1–10 mg/ml (Ansari and Ahmad, 1991).

18.3.3 LARVICIDAL EFFECT

Essential oil obtained from Zedoary was found to have promising potential to be used as a larvicide against *Aedes aegypti* mosquitoes with LD_{50} and LD_{99} of 33.45 and 83.39 ppm, respectively (Shiobara et al., 1985).

18.3.4 TOXICITY STUDY

Powdered *C. zedoaria* with high crude proteins proved lethal and caused 100% mortality at 320 g/kg body weight. Fresh rhizomes were found to be toxic at 400 g/kg of body weight in young rats (a week to 10 days old) but was only found to reduce the food intake capacity in one day old chicks when fed for 20 days (Latif et al., 1979).

18.3.5 ANALGESIC ACTIVITY

Fractions of hydroalcoholic extracts (dichloromethane; ethyl acetate (EA); methanol) were investigated for analgesic activity against standard drugs like aspirin and dipyrone. Several animal models, including models of pain

sensation in mice, including writhing, formalin, and capsaicin tests were used for the study. ID_{50} values were found to be 22 and 12 mmol/kg when evaluated in writhing and capsaicin tests, respectively, and 29 mmol/kg in relation to the second phase of the formalin model (Navarro et al., 2002).

18.3.6 ANTINOCICEPTIVE ACTIVITY

The antinociceptive effect of dichloromethane extracts of *C. zedoaria* was studied in mice at doses of 10 mg/kg administered intraperitoneally. It was found to show considerable antinociceptive activity (Hong et al., 2002).

18.3.7 ANTIALLERGIC ACTIVITY

80% aqueous acetone extract was found to prevent the release of beta-hexosaminidase and passive cutaneous anaphylaxis reaction in mice models (Matsuda et al., 2004).

18.3.8 ANTIULCER ACTIVITY

Rhizome powder at a dose level of 200 mg/kg reduced the gastric pH, free acids, total acids and ulceration index significantly when compared to Omeprazole (30 mg/kg i.p.) in rats (Raghuveer et al., 2004).

18.3.9 PLATELET ACTIVATING ACTIVITY

Aqueous extract of *C. zedoaria* was checked for its inhibitory effect on platelet activating factors using a radio-ligand. It was found to inhibit 50.60% of the platelet activating factor binding to functional platelets at a concentration of 200 mg/ml in rabbits. (Singh et al., 2002).

18.3.10 HEPATOPROTECTIVE ACTIVITY

Isolated hepatoprotective sesquiterpenes from the water acetone extract of *C. zedoaria* rhizome exhibited potent protective effect on D-galactosamine (D-GalN)/lipopolysaccharide (LPS)-induced acute liver injury in mice

(Matsuda et al., 1998). Dried rhizome extracts of *C. zedoaria* also inhibited cell proliferation and showed antifibrogenic effects toward hMF, indicated that ZR might have therapeutic implications in chronic liver disease (Kim et al., 2005).

18.3.11 ANTIVENOM ACTIVITY

Aqueous extract of rhizomes was investigated for inhibitory activity against cobra venom (CV) by binding of anti-cobra venom antibody to antigen of CV by using ELISA method. The extract of *C. zedoaria* showed effective inhibitory activity and was found to target the neurotoxin and protein-degrading enzyme present in venom (Sakda et al., 2005).

18.3.12 ANTI-INFLAMMATORY ACTIVITY

Chihiro et al. (2006) and Chachad and Shimpi (2008) studied anti-inflammatory activity using adjuvant arthritis mouse model carrageenan-induced paw edema in rats. However, *C. zedoaria* did not exhibit any significant activity in both of the above-said models using the methanolic and ethanolic extracts, respectively. But isolated compounds obtained from methanolic extracts were reported to suppress edema at the dose of 1 µmol (Makabe et al., 2006).

18.3.13 HEMAGGLUTINATING ACTIVITY

Crude proteins obtained from *C. zedoaria* exhibited Hemagglutinating activity against rabbit erythrocytes (Polkit et al., 2007).

18.3.14 ANTIMUTAGENIC ACTIVITY

Aqueous extract of *C. zedoaria* was studied for its potential antimutagenic activity by using the *Salmonella*/microsomal system in the presence of picrolonic acid or benzo[α]pyrene. It was found to possess moderate activity against benzo[α]pyrene (Lee and Lin, 1988).

18.3.15 ANTICANCER ACTIVITY

Water and alcoholic extracts of *C. zedoaria* were checked for cytotoxic activity against two types of human cancer cell lines and prostate cancer and one type of normal human cell line. The alcoholic extract of *C. zedoaria* was found to show cytotoxic activity against CORL-23 and PC3 but less

cytotoxic activity against 10FS. Water extract did not show any activity (Athima et al., 2005). Seo et al. (2005) investigated the inhibitory effect of aqueous extract of *C. zedoaria* on experimental pulmonary metastasis of B16 melanoma cells.

In terms of anticancer properties, previous studies showed that polysaccharides and protein-bound polysaccharides of *C. zedoaria* could inhibit the growth of sarcoma-180 (Moon et al., 1985; Kim et al., 2000; Lakshmi et al., 2011). Studies have also shown that the essential oil from *C. zedoaria* has an antiproliferative effect (Syu et al., 1998; Lay et al., 2004; Rahman et al., 2013).

18.3.16 ANTIOXIDANT ACTIVITY

Essential oil of *C. zedoaria* showed moderate to good antioxidant activity at 20 mg/ml and excellent scavenging effect on DPPH radical but low in chelating effect on ferrous ion (Mau et al., 2003).

KEYWORDS

- **antioxidant activity**
- ***Corynebacterium amycolatum***
- ***Curcuma zedoaria***
- **essential oils**
- **ethyl p-methoxycinnamate**
- **human cancer cell lines**
- **white turmeric**

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CHAPTER 19

Phytochemical and Pharmacological Profile of *Cymbidium aloifolium* (L.) Sw.

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19.1 INTRODUCTION

Cymbidium aloifolium (L) Sw. is an epiphyte, native to tropical and subtropical Asia. It is distributed in Bangladesh, China, India, Indonesia, Japan, Kenya, Myanmar, Mexico, Madagascar, Mauritius, Malaysia, Nepal, Peru, Philippines, Sri Lanka, Singapore, Thailand, Vietnam, and Tropical humid forests of Central and South America (Liu et al., 2009; Hossain, 2009). It flowers during March–June. It is called boat orchid in English, *supurn* in odisha, *panaipulluruv*i in Tamil and *Thit tet lin nay* in Myanmar (Teoh, 2016). In this chapter, an attempt has been made to review the phytochemical and pharmacological importance of *C. aloifolium*.

19.1.1 ETHNOMEDICINAL USES

1. **Aerial Roots:** The paste of aerial roots used to treat foot krack, fractured bones by Koyas and Konda reddis of Eastern Ghats, India (Rajendran et al., 1997; Reddy et al., 2005) and Tanchinga tribe of Bangladesh (Hossain, 2009), cement broken bones by Koyas of Khammam forest area, India (Raju et al., 2008); rheumatism and nervous disorders by local community of Nepal (Subedi, 2011;

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Subedi et al., 2013); paralysis by Dongria Kandha tribe of Orissa, India (Dash et al., 2008).

2. **Whole Plant:** In Indian folk medicine, juice extracted from the whole plant mixed with ginger and some amount of water has been used to induce vomiting and diarrhea (Caius, 1936). The paste of the whole plant is used to treat burns, purgative, emetic, and ear aches in the Arunachal Pradesh area (Chowdhery, 1998).
3. **Leaves:** Leaf juice is used for Ear disease by Kurumbas of Tamil Nadu (Balasubramanian et al., 2000), boils and fever, and Ear ache, cut, and wounds by Tanchinga and Tripura tribes of Bangladesh (Hossain, 2009; Mukul et al., 2007), Ear diseases by Irula, Muthuva tribes of Kerala (Shanavaskhan et al., 2012). Leaf paste is used for Epilepsy and Memory enhance by Khamathi community in Arunachal Pradesh (Chowlu et al., 2017). Crushed leaves are used to stop bleeding from leech bites (Rao and Sridhar, 2007).
4. **Tuber:** The paste is used to treat wounds, skin diseases by the Malayali tribe in Tamil Nadu (Xavier et al., 2015).
5. **Seeds:** The paste is used to treat Healing wounds by Garos, Nagas, Kukis, Khasis, and Bodos of the Assam region (Medhi and Chakrabarti, 2009).

19.2 BIOACTIVE COMPOUNDS

A total of 11 phytochemicals, such as flavonoids, phenols, quinones, coumarins, saponins, alkaloids, carbohydrates, tannin, cardiac glycosides, oxalates, gum, and mucilage were present in various solvent extracts of the *C. aloifolium* parts (Radhika et al., 2013; Shubha and Chowdappa, 2016; Rampilla and Khasim, 2020; Bowmik et al., 2020). Qualitative analysis (Through GC-MS) of various organic extracts showed that eight different photochemical compounds (Table 19.1) namely n-Hexadecanoic acid, 9,12-Octadecadienoic acid (Z,Z), 9,12,15-Octadecatrienoic acid, (Z,Z,Z), Octadecanoic acid, Phytol, 2-Butyne, 2-Cyclopenten-1-one, 1,4-Benzenedicarboxylic acid (Rampilla and Khasim, 2020).

The phenanthrenes are aromatic metabolites which are presumably formed by oxidative coupling of the aromatic rings of stilbene precursors. Juneja et al. (1987) identified several phenanthrenes such as aloifol I and II, coelonin, and 6-methoxycoelonin. The other phytocompounds like cymbinodin A (Barua et al., 1990), cymbinodin B (Ghosh et al., 1992), a novel polyoxygenated phenanthrene derivative designated pendulin. Dey et al. (1998) isolated and

crystallized phenanthraquinone derivative 1,2,3,7-tetramethoxy-5,6-phenanthraquinone, from *C. aloifolium.* It also contains two substituted bibenzyls, dihydrophenanthrene, and phenanthraquinone (Cymbinodin-A), which are responsible for biological activity (Hossain, 2009).

TABLE 19.1 Bioactive compounds of *Cymbidium aloifolium*

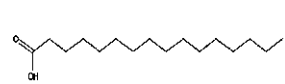
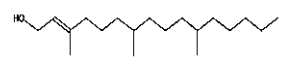
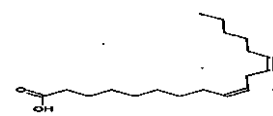
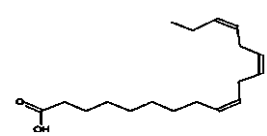
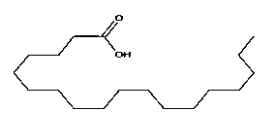
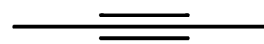
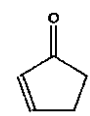
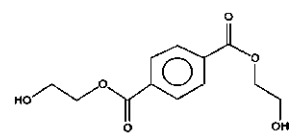
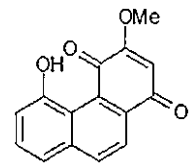
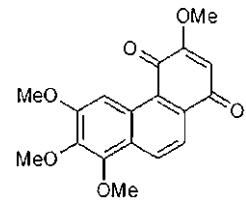
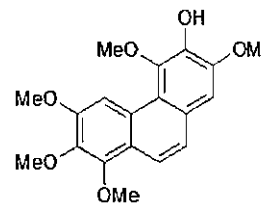
Name of the Compound	Nature of the Compound	Molecular Formula	References
n-Hexadecanoic acid	Palmitic acid (saturated fatty acid)		Rampilla and Khasim (2020)
Phytol	Acyclic, diterpene		Rampilla and Khasim (2020)
9,12-Octadecadienoic acid (Z,Z)-	Linoleic acid		Rampilla and Khasim (2020)
9,12,15-Octadecatrienoic acid, (Z,Z,Z)-	Linolenic acid ester		Rampilla and Khasim (2020)
Octadecanoic acid	Stearic acid		Rampilla and Khasim (2020)
2-Butyne	Alkyne		Rampilla and Khasim (2020)
2-Cyclopenten-1-one	Ketone		Rampilla and Khasim (2020)
1,4-benzenedicarboxylic acid, bis(2-hydroxyethyl) ester	Ester		Rampilla and Khasim (2020)
Coelonin (tri substituted dihydro/phenanthrenes)	Aromatic hydrocarbons (phenanthrene)	–	Lv et al. (2020)
6-methoxycoelonin	Aromatic hydrocarbons (phenanthrene)	–	Juneja et al. (1987)

TABLE 19.1 *(Continued)*

Name of the Compound	Nature of the Compound	Molecular Formula	References
Cymbinodin-A	Aromatic hydrocarbons (polyoxygenated phenanthrene)		Barua et al. (1990)
Cymbinodin-B	Aromatic hydrocarbons (polyoxygenated phenanthrene)		Ghosh et al. (1992)
Pendulin	Aromatic hydrocarbons		Majumder and Sen (1991)

19.3 PHARMACOLOGICAL ACTIVITIES

19.3.1 ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES

The ethanol leaf extract of *Cymbidium aloifolium* showed both analgesic activity and anti-inflammatory activity. Analgesic activity was determined by acid induced writing test in mice test. The test results showed a statistically significant reduction of the percentage of writhing of 33.57 and 61.31% at 200 and 400 mg kg(–1) oral dose. Carrageenan induced paw edema test used to determine anti-inflammatory activity. The ethanolic plant extract also showed significant dose dependent reduction of mean increase of formation of paw edema. The results of the experiment showed that the ethanolic plant extract had shown significant dose dependent analgesic and anti-inflammatory activities when compared to the control (Howlade et al., 2011).

19.3.2 ANTIMICROBIAL ACTIVITY

Radhika et al. (2013) studied antimicrobial activity of hexane, chloroform, and methanol leaf extracts in three different concentrations (100, 250, 500

mg/ml) against 10 potential clinical pathogenic bacteria namely *E. coli, Proteus vulgaris, Xanthomonas* sps., *Pseudomonas mirabilis, Pseudomonas aeruginosa, Klebsiella oxytoca, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus mitis, Staphylococcus anginosus*. Chloroform extract showed more effective on test organisms than the methanol and hexane extracts.

The methanol and acetone extracts of *C. aloifolium* capsule cover showed the maximum antibacterial activity against *B. subtilis, E. coli, P. aeruginosa* and *S. aureus.* Capsule cover acetone extract exhibited MIC and MBC at 1.87 mg/ml and 3.75 mg/ml against *K. pneumoniae*; 0.312 and 0.625 mg/ml against *B. subtilis*; 2.5 and 10 mg/ml against *E. coli* and *P. aeruginosa*; 0.125 and 0.25 mg/ml against *S. aureus* (Shubha and Chowdappa, 2016).

19.3.3 ANTIOXIDANT ACTIVITY

Soumiya and Williams (2018) screened the antioxidant activity of different organic flower extracts (methanol, ethanol, chloroform, acetone, and aqueous) of *C. aloifolium* by nitric oxide (NO) radical scavenging activity. Results conclude that aqueous and ethanol extract was more active than other extracts.

19.3.4 CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANT EFFECTS

The ethanolic leaf extract, at the dose of 200 and 400 mg/kg body weight, were shown to have CNS depressant activity by the reduction of locomotor and exploratory activities in the open field and hole cross tests (Howlader and Alam, 2011).

19.4 GAPS AND FUTURE RECOMMENDATIONS

More evidence-based studies are required with regarding to Ethnobotany. The parameters such as exploration of ethnic group, Formulation, doses, patient description and usage frequency of the plant against disease are needed to document. Pharmacological activities are very less explored in this plant. *In-Vivo* studies on animal models, clinical, and mechanism-based studies should be performed to prove mechanism linked to ethnobotanical uses.

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KEYWORDS

- **antimicrobial activity**
- **central nervous system**
- ***Cymbidium aloifolium***
- **ethanolic leaf extract**
- **phytochemicals**
- ***Pseudomonas aeruginosa***
- **radical scavenging activity**

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CHAPTER 20

Phytochemicals and Pharmacological potentialities of Lemongrass [*Cymbopogon flexuosus* (Nees ex Steud.) W.Watson]

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20.1 INTRODUCTION

Cymbopogon, a member of the family Poaceae comprised of about 140 species widely distributed across the world. They are the indigenous herbs of tropical and sub-tropical areas of Asia, and used as cultivar of South and Central Africa and America and also known worldwide for their high content of essential oils (EOs). *Cymbopogon flexuosus*, an aromatic and medicinally important herb reported as native to the Indian subcontinent (originated from the Western Ghats of India) but also recorded as native in Myanmar and Thailand (Ganjewala and Gupta, 2013). Synonyms of the species include *Cymbopogon travancorensis* Bor, *Andropogon nardus* L. var. *flexuosus* (Nees ex Steudel) Hackel, *Andropogon flexuosus* Nees ex Steudel (Singh et al., 2016). The common names of this herb are East Indian grass, Lemongrass, Cochin, or Malabar grass. In India, This herb grows in the wild in most of regions, where sunny and humid conditions and also from sea level to 900 m asl and produces the higher oil yield/ton (Skaria et al., 2006). Large-scale cultivation of this grass has been undertaken by Australia, Thailand, Europe, Mexico, Dominica, Haiti, Madagascar, Guatemala, Indonesia, and China (Husain et al., 1988; Ganjewala and Gupta, 2013). The herbaceous parts of

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C. flexuosus was reported to contain 0.2–0.4% oil by distillation with oil yield of 100–125 kg/ha/year (Weiss, 1997; Skaria et al., 2006). Lemongrass is considered a ratoon crop, fast-growing, and usually exhibits tiller growth (Ganjewala and Gupta, 2013). Drought-tolerant, multi-harvest, perennial numerous erect culms having reddish or whitish color, smooth, and glabrous in texture originating from short, thick rhizome. This plant produces flowers at matured stages of growth with a loose, large, repeatedly branched panicle, along with numerous long flexuous drooping branches (Weiss, 1997; Jaganath and Ng, 2000; Sugumaran et al., 2005; Ganjewala and Gupta, 2013).

Cymbopogon flexuosus var. *flexuosus* is commonly known as red grass due to its peculiar morphology of reddish or purple stem and leaf sheath. Moreover, *C. flexuosus* var. *flexuosus* has renowned for its highly prized EOs and commercially cultivated for flavor and fragrance industries, which has exhibited solubility in organic solvent like alcohol, so it is considered as superior among *Cymbopogon* species. The essential oil of *C. flexuosus* contains citral (> 65–70%) which exhibited poor solubility in alcohol (Guenther, 1950; Weiss, 1997; Skaria et al., 2006). The oil of *C. flexuosus* has mainly been used for the isolation of citral, and utilized for the synthesis of a number of industrial chemicals (Nair, 1982). This oil has also been used in aromatherapy, culinary flavoring, perfumery, cosmetics, and beverages along with numerous biological activities as analgesic, antiseptic, carminative, astringent, febrifuge, fungicidal, bactericidal properties and used in digestive tract spasms, stomach ache, hypertension, convulsions, pain, cough, rheumatism, period cramps, ringworm, athlete's foot, toothache, migraine, fever, common cold, vomiting, etc. (Skaria et al., 2006; Singh et al., 2016; Ganjewala, 2009).

20.2 BIOACTIVES

The genus *Cymbopogon* is unique among grasses in possessing oils in all parts of the plant (Gupta, 1969). The oil obtained from lemongrass is lemon-scented, pale yellow or dark yellow and dark-amber viscous liquid. (Skaria et al., 2006; Singh et al., 2016). The EOs obtained from lemongrass are reported with a variety of chemical components. The GLC and GC-MS investigation of oil has indicated the presence of large amount of monoterpenes (Rajendrudu and Das, 1983). Kumar et al. (2009) reported the dominant components of lemongrass oil were as limonene, myrcene, citral, citronellal, citronellol, terpineol, methyl heptenone, dipentene, geraniol, geranial, geranyl acetate, neral, nerol, and farnesol (Nath et al., 1994; Ganjewala, 2009; Avoseh et al., 2015). Singh et al. (1991) proved the synthesis and accumulation of citral

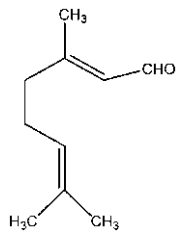
content were dependent on the ontogeny of the leaves and alteration in the essential oil content has directly reflected in the changes of citral content.

Sarma et al. (1999) have reported elemicin (53.0%) as a major constituent among 50 compounds identified from the oil, followed by limonene (11.6%), beta-ocimene (7.6%), camphene (4.1%) and 1-epi cubenol (3.9%). Nath et al. (2002) revealed the chemical composition of oils from inflorescence of four varieties of *C. flexuosus,* in which methyl eugenol ether, citral, elemicin, and citronellol were found as major constituents. Pandey et al. (2003) reported geranyl acetate (5.27%), citral (43.80%), trans-geraniol (3.66%), z-citral (18.93%) as dominant compounds from *C. flexuosus*. The investigation on morphological characters and yields characteristics of oil and Citral content in a few lemongrass varieties grown in different agro-climatic regions of Northeast India was carried out by Sarma and Sarma (2005). Citral (78.0–95.0%) was recorded as the major compound and found as maximum in the winter season whereas; it was minimum at rainy season. Luthra et al. (2007) recorded acyclic monoterpenes, citral (83%) from steam-distilled aerial parts of *C. flexuosus* (cultivar OD-19). Geraniol was also found to be the major component from the mutant variety of *C. flexuosus* (cultivar GRL-1). Ganjewala et al. (2008) investigated the compositions of oil in eight cultivars of *C. flexuosus,* which revealed that the chief component of seven cultivars as citral (75–85%), and geraniol (90%) have described as the key component. The essential oil of the leaf of *C. flexuosus* is mainly composed of citral with 80–84% of the total monoterpene content (Kakarla and Ganjewala, 2009). Chowdhury et al. (2010) have isolated and analyzed the chemical components of oil isolated from *C. flexuosus* collected from Kumaon, Uttrakhand. Gas chromatography-mass spectroscopic investigation of essential oil revealed 34 compounds with 97.9% of the total oil. The main chemical constituents of the oil were linalool (2.6%), citral-b (30.0%), citral-a (33.1%) and geranyl acetate (12.0%).

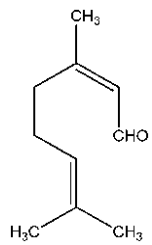
Adinarayana et al. (2012) characterized the chemical composition of field distilled essential oil, in which, the major chemical compounds were identified as 6-methyl hept-5-en-2-one (1.93%–32.89%), (Z)-citral (1.96%–34.8%), (E)-citral (12.32%–42.07%), and geraniol (0.44%–5.08%). The essential oil distilled from the field has showed predominance of (Z) and (E)-citral while the notable compound was 6-methyl hept-5-en-2-one. Desai and Parikh (2012) have analyzed the components of oil by Gas Chromatography-Mass Spectroscopy, in which more amounts of oxygenated compounds were recorded.

Singh et al. (2016) have isolated essential oil from the region of Western Uttar Pradesh and revealed the composition with large amounts of monoterpenes (93.4%) alcohols (54.4%), aldehydes (31.7%), ester (0.7%) and hydrocarbons (6.7%), in which, pre-dominant monoterpenes were geraniol (51.7%), geranial (29.0%), α-pinene (4.8%). citronellal (1.3%), citronellol (1.2%), myrcene (1.1%) and trans-verbenol (1.0%). Gupta et al. (2016) have investigated the chemical components of EOs of three cultivars Suvarna, Pragati, and Praman of *C. flexuosus*. The EOs isolated from these varieties were characterized by the presence of monoterpenes such as, Geranial (citral a) (53%), Neral (citral b) (29%), Geraniol (2%) and Geranyl acetate (1%). A considerable number of investigations were attempted on the analysis of chemical components of oil isolated from *C. flexuosus,* revealed the presence of large amounts of monoterpenes.

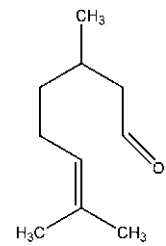
Phytochemicals in *Cymbopogon flexuosus*



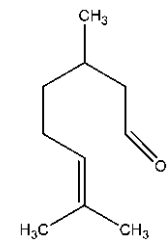
Citral a



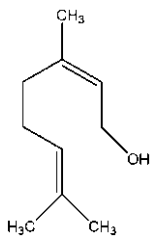
Citral b



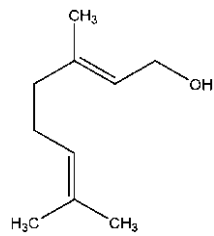
Citronellal



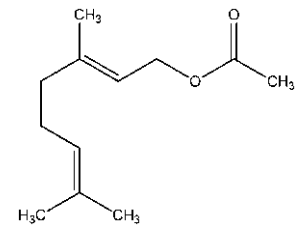
Citronellol



Nerol



Geraniol



Geranial

20.3 PHARMACOLOGY

20.3.1 ANTIMICROBIAL ACTIVITY

Chao et al. (2000) investigated the antifungal and antibacterial efficiency of essential oil of *C. flexuosus* which helps to recover from stress-related

disorders. They screened lemongrass oil against bacteria, fungi, and viruses, in which lemongrass oil has exhibited higher antimicrobial efficiency with broadest range of inhibition. Suhr and Nielson (2003) recorded the antifungal properties of essential oils (EOs) of *C. flexuosus* against bread spoilage fungi. Kakarla and Ganjewala (2009) evaluated the antibacterial potential of four varieties of *C. flexuosus* such as Pragati, Krishna, Suvarna, and Neema, in which citral in a single form and in a combination of honey was evaluated against three multi-drug resistant bacteria *Staphylococcus aureus, Pseudomonas aeruginosa* and *Acinetobacter baumannii* using well diffusion method. The study has revealed that essential oil of Krishna (44–50 mm/50 µL) has potent bactericidal properties than others. The EOs of Pragati and Suvarna were selectively effective against *S. aureus*, whereas of Nima against *A. baumannii* and *P. aeruginosa.* Citral has exhibited better activity against screened bacteria with considerable inhibitory zone (38–45 mm/50 µL). The combined effect of all four EOs along with honey showed better antibacterial activity against *S. aureus.*

Essential oil isolated from *C. flexuosus* was found as efficient against the growth of fungi and aflatoxin production. The essential oil has inhibited the growth of *Aspergillus flavous* and aflatoxin B1 production. Eugenol was proved as potent against fungi and aflatoxin inhibitory activity. The essential oil isolated from *C. flexuosus* can be utilized as plant based antimicrobial to control bio-deterioration of herbal raw materials (Kumar et al., 2009). Adinarayana et al. (2012) evaluated antimicrobial efficiencies of field distilled oil and water-soluble oils against pathogenic fungi and bacteria by agar disc diffusion method. All the samples exhibited potential activity against tested bacteria and fungi. Among the organisms screened, *Staphylococcus aureus* was considered as most effective at 250.5 µg/ml and inhibited complete growth. *Aspergillus niger* was found to be resistant to all samples with slight variation in MIC value. The difference in activity was ascribed to the presence of varied permeability of mycelial growth and spore walls of different fungi. Adukwu et al. (2012) investigated the anti-biofilm efficiency of EOs of *C. flexuosus* and *Citrus paradisi* against 5 strains of *Staphylococcus aureus.* Lemongrass oil exhibited the most effective antimicrobial and anti-biofilm activity.

Ahmad and Viljoen (2014) carried out the antimicrobial efficiency of six different *Cymbopogon* EOs alone and in combination with silver ions against *Escherichia coli, Enterococcus faecalis, Moraxella catarrhalis, Staphylococcus aureus, Candida albicans,* and *Candida tropicalis*. The higher activity was recorded in *C. flexuosus* essential oil with Ag^{+} against *C. albicans*. The construction of iso-bolograms and time-kill plots were

used for the confirmation of the synergistic interaction. Chaisripipat et al. (2015) identified the inhibitory action of essential oil against dandruff yeast, *Malassezia furfur* (MIC of 6.70 ppm). Adukwu et al. (2016) determined the cytotoxic effect of *C. flexuosus*, which revealed the potentialities of essential oil and citral on inhibiting and damaging MDR *A. baumannii*. The higher antimicrobial efficiency of essential oil of lemongrass is attributed to higher citral content (Adukwu et al., 2012).

Singh et al. (2016) carried out antimicrobial activity against *Aspergillus niger*, *Staphylococcus aureus*, *Candida albicans* and *Escherichia coli* by agar-well-diffusion method. *Aspergillus niger* (10.2 mm) was found to be susceptible with minimum inhibitory zone. *Escherichia coli* (12.8 mm), *Candida albicans* (12.5 mm) were reported with moderate resistance to oil followed by *Staphylococcus aureus* (15.3 mm). The antimicrobial potentialities of EOs isolated from three cultivars (Suvarna, Pragati, and Praman) of *C. flexuosus* and were studied by Gupta et al. (2016). The study has revealed the antimicrobial effects of essential oil from Suvarna against bacteria (29–38 mm) and fungi (28–30 mm). The antimicrobial effects of aqueous extract of *C. flexuosus* leaves were studied by Ooi et al. (2019), in which, the water extract exhibited better bactericidal activity against *Staphylocuccus aureus* and *Escherichia coli* by the constant decrease in absorbance and the elimination of viable counts at 1 h.

20.3.2 ANTICANCER ACTIVITY

Sharma et al. (2009) suggested innovative therapeutic strategies of oil obtained from *C. flexuosus* against cancer. *In vitro* cytotoxicity assay against 12 human cancer cell lines and *in vivo* anticancer activity of oil was attempted against solid and ascitic Ehrlich and Sarcoma-180 tumor models in mice. Morphological changes in tumor cells have been screened to understand the mechanism of cell death. The various constituents reported from the oil of *C. flexuosus* such as bisabolol (8.42%), geraniol (20.08%), isointermedeol (24.97%) and geranyl acetate (12.20%) have been individually reported for their cancer cell cytotoxicity (Carnesecchi et al., 2001; Kumar et al., 2008).

20.3.3 ANTI-INFLAMMATORY AND ANALGESIC EFFECT ACTIVITIES

Chandrashekar and Prasanna (2010) bared the pioneer pharmacological screening and clinical trials on Analgesic and anti-inflammatory efficiencies

of essential oil of *C. flexuosus* using animal models. The essential oil showed significant dose-dependent anti-inflammatory activities in acute carrageenan-induced rat paw edema and the chronic granuloma pouch models. The analgesic efficiencies of essential oil were studied in acetic acid-induced writhing exhibited maximum activity at 200 mg/kg. On the other hand, the study disclosed negative result on tail-flick model.

Han and Parker (2017) validated the anti-inflammatory potentialities of commercially available essential oil of *C. flexuosus* in pre-inflamed human dermal fibroblast cells. The study suggested that the oil has good therapeutic factor to treat inflammation of the skin. Also, studied the impact of oil on 17 protein biomarkers critically associated with inflammation and tissue remodeling and genome-wide gene expression profiles.

20.3.4 ANTI-ULCER ACTIVITY

Adikay and Santhoshini (2015) demonstrated the anti-ulcer activity in animal model. The ethanol extract obtained from the leaves of *C. flexuosus* was evaluated through pylorus ligation in rats. There was a significant reduction observed on the acid volume, total acidity and free acidity in animals treated with ethanol extract (400 mg/kg). The study demonstrated that the ethanol extract has potent anti-ulcer activity on pylorus ligated-induced ulcers in rats.

20.3.5 ANTI-DEPRESSANT ACTIVITY

Nomier et al. (2021) investigated antidepressant and anxiolytic profiles of ethanolic extract of dried leaves *C. flexuosus* in chronic unpredictable mild stress-induced in adult female Wistar rats. Antidepressant and anxiolytic activities were attempted by elevated plus maze, activity box, light, and dark box and open field activity. The treatment with 100 mg/kg ethanolic extract has shown best results when exposed to a schedule of chronic mild stress over a period of 14 days.

The literature survey carried out in the plant has been revealed that the phytochemical and pharmacological potentialities of *C. flexuosus* are scanty. Still, there are areas that need to be explored and substantiate the bioactive potential of lemongrass oils and evaluation of them both *in vivo* and *in vitro* activities. Further, investigations are needed to assess the molecular studies and therapeutic potential of highly active compounds.

KEYWORDS

- **anxiolytic profiles**
- ***Aspergillus flavous***
- **citral**
- ***Cymbopogon flexuosus***
- ***Enterococcus faecalis***
- **essential oil**
- **Lemon grass**

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CHAPTER 21

Biochemicals and Biological activities of *Cymbopogon jwarancusa* (Jones) Schult.

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21.1 INTRODUCTION

Cymbopogon jwarancusa (Jones) Schult. belonging to Poaceae is found in tropical and temperate areas of India, Bangladesh, Pakistan, Nepal, Iraq, and in several other countries. An essential oil in low amount with mint smell is present in the plant. In traditional systems of medicine, almost all parts are used. However, roots, and shoots are more important medicinally. This plant is known differently in various languages and regions of the country. It is named as "Lamajjakai" in Sanskrit; in Hindi and Punjabi as "Khavi, Bur," and in English "Camel grass." The specific name *jwarancusa* seems to have been derived from "Jwar" meaning fever and "Kusha" meaning grass, i.e., grass curing fever, and Stapf (1906) referred *C. jwarancusa* as being employed in all types of fevers.

It is a tall grass with roots that are aromatic. Leaves are broad and flat, filiform, and linear above, with a long capillary tip. Culm erect, nodes often swollen. Leaf sheath glabrous, more or less curled. Leaf blade whitish and glabrous. Panicle erect, spikelet is sessile and measures about 4.5–5.5 mm. Lower glume is sharply keeled, lanceolate, and concave on the back,

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glabrous, nerveless or 1–2 nerved; Pedicelled spikelet is slightly longer (6 mm) with a lanceolate lower glume, 3–7-nerved.

The plant is traditionally used in Unani medicine. A wide number of phytochemicals have been isolated from the plant with a good number of pharmacological properties.

21.2 BIOCHEMICALS

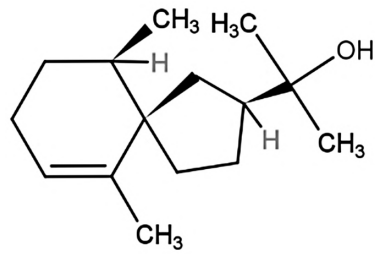
The various parts of the plant possess essential oil, piperitone being the essential constituent. Cadinene, borneol, camphene, camphor, geraniol, farnesene, α and β-pinene are also present., was investigated by using glass capillary gas chromatography in combination with mass spectrometry the composition of the essential oil of *Cymbopogon jwarancusa* was analyzed. Of the 64 compounds identified, 55 are reported for the first time (Saeed et al., 1978). The smell of this grass is due to the high percentage of piperitone (60–70%) (Saeed et al., 1978). Agarospirol is the largest sesquiterpenoid component in the root oil of *C. jwarancusa* (Shahi and Tava, 1993). Beauchamp et al. (1996) reported the content of sesquiterpenoid *(*38.0%.) in the root oil of *C. jwarancusa*

Chemical analysis of the plant revealed the following parameters – moisture content, 67.02%; ash content, 9.52%; carbohydrates, 1.8%; reducing sugar, 1.07%; non-reducing sugar, 0.80%; nitrogen, 0.67%; crude proteins, 5.02%; crude fiber, 9.50%. Extracted seed oil indicated acid value, 7.32%; iodine value, 1.6%; saponification value, 155.25%; peroxide value, 18.2%; refractive index, 1.432 and pH of extracted oil was 4.45. Trace element analysis showed sodium 0.60%, potassium 0.20%, lithium below detection limit, nickel 0.21%, lead 0.34%, cadmium 0.12%, zinc 0.98%, copper 0.10%, manganese 1.25%, iron 1.37% and cobalt 0.31% (Mahmud et al., 2002).

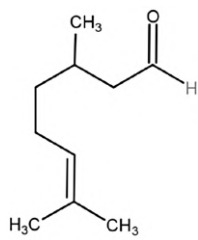
The major trace constituents of the EOs of *C. jwarancusa* include terpenes-piperitone and Δ-carene; citronellal, *p*-cymene, geraniol, β-pinene, and γ-terpinene. Traces include alloaromadendrene, *cis*-, and γ-allo-ocimene, α-bisabolene, β-bisabolene, borneol, *d*-cadinene, calamene, camphene, camphor, β-caryophyllene, β-caryophyllene oxide, α-chamigrene, 1,8-cineole, citronellol, α-cubebene, cuprene, *o*-cymene, 5,6-dimethyl-5-norbornen-2-ol, dipentene, β-elemene, *d*-elemene, elemol, eucarvone, eudesmol, α-farnesene, β-farnesene, fenchone, geranyl acetate, geranylformate, geranyl propionate, germacrene, α-humulene, iso-borneol, kasuralcohol, lavendulol, linalool, longifolene, *cis*-, and γ-*p*-mentha-2-en-1-ol methyl

heptenone, *p*-mentha-2,8-dien-1-ol, methyl thymyl ether, α-muurolene, myrcene, myrtenal, phellandrene, α-pinene, γ-and *cis*-peperitol, terpinen-4-ol, α-terpineol, terpinolene, γ-thuj-2-en-4-ol, verbenone, and β-ylangene (Akhila, 2010).

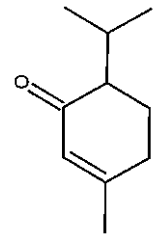
Bhuyan et al. (2010) reported that major constituents of essential oil of *C. jwarancusa* include linalool, citral-a, citral-b, geraniol, and elemol. However, only two components viz., piperitone (54.36%) and α-phellandrene (30.86%) were reported by Bose et al. (2013).



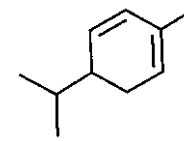
Agarospirol



Citronellal



Piperitone



Phellandrene

21.3 BIOLOGICAL ACTIVITIES

21.3.1 ANTI-HYPERLIPIDEMIC AND ANTI-HYPERGLYCEMIC ACTIVITIES

Different doses of ethanol leaf extract of *C. jwarancusa* have been investigated for anti-hyperglycemic and anti-hyperlipidemic activities in rats by measuring body weight, fasting blood glucose levels and serum lipid profile. Significant dose dependent reduction in body weight, blood sugar levels and lipid parameters were observed (Khan et al., 2018a).

21.3.2 ANTI-INFLAMMATORY ACTIVITY

Ethanolic leaf extract of *C. jwarancusa* was studied in rats at different doses using carrageenan induced paw edema model for anti-inflammatory activity. The findings showed that leaves had significant dose dependent reduction in paw edema at the 4th hour and highly significant reduction at the 5th hour. The percentage inhibition of edema was 38.16%, 43.46% and 44.35, respectively at the 5th hour at 150, 300, and 500 mg/kg of plant extract (Sarah et al., 2018).

21.3.3 CYTOTOXICITY

In vitro cytotoxicity of *C. jwarancusa* oil and its constituents was evaluated by Sulforhodamine-B assay on human cancer cell lines THP-1 (leukemia), A-549 (lung) HEP-2 (liver) and IGR-OV-1 (ovary). The oil was found to be more potent than its constituents against cancer cell lines tested with IC_{50} of 6.5 µg/ml (THP-1), 6.3 µg/ml (A-549), 7.2 µg/ml (HEP-2) and 34.4 µg/ml (IGROV-1) (Dar et al., 2011).

21.3.4 FLUKICIDAL ACTIVITY

Different concentrations of crude methanolic extracts were tested on live adult flukes viz; *Paramphistomum cervi* and *Fasciola gigantica* isolated from liver and bile ducts of slaughtered buffalo. Inhibition of motility and paralysis leading to the death of parasites was noticed. Thus significant flukicidal activity compared to positive control was observed. Furthermore, ED_{50} for *C. jwarancusa* against *F. gigantica* and *P. cervi* were 13.1 and 10.8 mg/ml, respectively (Andeela et al., 2015).

21.3.5 DIURETIC ACTIVITY

Diuretic activity was assessed by using different strengths of ethanol extract of *C. jwarancusa*. The response of test drug was assessed by using furosemide as reference drug. Significant diuretic effect was noticed (*C. jwarancusa* at a dose of 500 mg/Kg single and multiple doses). As compared to control, 300 mg/Kg extract displayed significant diuretic response only on 3rd and 4th day (Khan et al., 2018b).

21.3.6 ANTI-MICROBIAL ACTIVITY

Antibacterial, antifungal, and antiyeast activities of *Cymbopogon* essential oils (EOs), e.g., geraniol, citronellol, citral, citronellal, and piperitone, were assessed (Ganjewala, 2009). Essential oil from *C. jwarancusa* appear to be significant in *in vitro* control of two rice pathogens *Rhizoctonia solani* and *Bipolaris oryzae* which causes sheath blight and brown spot disease of rice, respectively (Bhuyan et al., 2010).

The preliminary antimicrobial screening of *C. jwarancusa* leaves (water and ethanol extracts) on *Aspergillus flavus, Fusarium oxysporum, Staphylococcus aureus* and *Streptococcus salivarius* gave relatively wide inhibition zones against the test strains as compared to positive control. The ethanol extract showed very wide zone of inhibition against *Fusarium oxyporum* f. sp. *lini* (85.31 ± 0.25 mm) and *Staphylococcus aureus* (94.37 ± 0.28 mm) at 500 ppm concentration in comparison to other strains. Water extract was found very less effective against *Aspergillus flavus* (03.72 ± 0.19 mm) at 100 ppm concentration (Prasad et al., 2011).

The essential oil markedly suppressed the growth of several species of *Citrobacter, Klebsiella pneumoniae, Proteus mirabilis, Salmonella enteric* ser. *typhi* and *Shigella flexneri* at the dose of 105 CFU/ml. by the antimicrobial assay using agar well diffusion method. The most active compounds among the 19 examined, 6 constituents showed antibacterial activity. Among the 6 constituents, geraniol completely inhibited the growth of bacteria than fungi. The β-pinene, linalool, and α-terpeniol showed an inhibitory activity against some bacteria and fungi, whereas the other compounds lacked this property (Bose et al., 2013).

21.3.7 ANTIOXIDANT ACTIVITY

Water and ethanol extracts of *C. jwarancusa* exhibited powerful antioxidant activity in various antioxidant systems *in vitro*. The water extract showed highest antioxidant activity (54.76 ± 1.37%) at 1 mg/10 ml concentration while the ethanol extract showed highest antioxidant activity in DPPH (31.99 ± 0.50% inhibition) and FRAP (38.79 ± 0.54 Fe (II)μL) assay (Prasad et al., 2011).

21.4 CONCLUSION

Cymbopogon jwarancusa is a very important plant for its large number of medicinal properties as well as medicinally important chemicals like citronellal, piperitone, geraniol, pentatriacontane, 6-pentatriacontanone, elemal. The plant showed many pharmacological activities like antioxidant, anti-allergic, antimicrobial, and antiparasitic. Many traditional uses are also reported like antiperiodic, purgative, and antioxidant, in various types of illness which are being studied till today and further research has to be done. Thus, *Cymbopogon jwarancusa* is a quite promising multipurpose medicinal plant.

KEYWORDS

- **antimicrobial assay**
- **antioxidant activity**
- ***Aspergillus flavus***
- **citronellal**
- **crude methanolic extracts**
- ***Cymbopogon***
- ***Staphylococcus aureus***

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CHAPTER 22

Phytochemical Constituents and Pharmacology of *Decalepis arayalpathra* (J. Joseph & V. Chandras.) Venter

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22.1 INTRODUCTION

Decalepis arayalpathra (J. Joseph & V. Chandras) Venter (Syn.: *Janakia arayalpathra* J. Joseph & Chandras) belongs to the family Apocynaceae. *D. arayalpathra* is a rare and endemic species found in the crevices of rocks in the southern Western Ghats region of Kerala, India (Joseph and Chandrasekharan, 1978; Pushpangadan et al., 1990). It is locally known as *Amruthapala* in Malayalam and *Amirtha palam* in Tamil. The Kani tribes use the root of this plant species to cure gastric ulcers, cancer-like symptoms, and as a rejuvenating tonic. In the *Oushadha Nighantu* (a Malayalam Ayurvedic literature on medicinal drugs) published by Mr. Tayyil Kumaran Krishnan in 1906, the plant *D. arayalpathra* is referred to as *Mritha Sanjeevini* (the

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drug that may restore the unconscious or dead) or *Sanjeevini* or *Thampra Rasayani* (Pushpangadan et al., 1990).

It is a woody shrub with root tuberous, strongly smelling. Stem, leaf-stalks and leaves reddish brown. Leaves are like that of peepal, 4–6.5 x 2–3.5 cm, ovate, apiculate at tip, round to broadly attenuate at base, entire or slightly wavy on margins; vein reticulations prominent on lower side; leaf-stalks 2.5–3 cm long. Small flowers are borne in axillary cymes, carried on slender, 2–3 cm long stalks. Calyx is bell-shaped tube about 0.1 cm long, sepals 5, 0.05–0.1 cm long, ovate. Stamens 5 carpels 2, apocarpous; ovules many in each carpel; stigma 5-angled. Follicles are linear, 3–3.5 cm long, 0.5–0.6 cm diameter, cylindric, tip tapering. Seeds many, 0.5–0.6 cm long, 0.25–0.3 cm wide, laterally compressed, winged on margins; wings variously curved; coma of white silky hairs 1.5–1.8 cm long (Joseph and Chandrasekharan, 1978; Lekshmi et al., 1992).

22.2 PHYTOCHEMICAL CONSTITUENTS

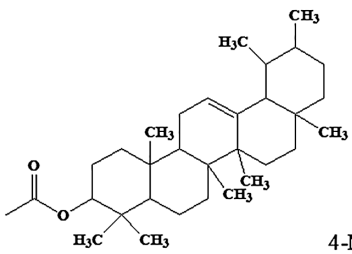
The compounds isolated from *D. arayalpathra* include, α-amyrin acetate, 4-methoxy salicylaldehyde, magnificol (12,20(29)-lupadien-3-ol), β-sitosterol, 3-hydroxy-p-anisaldehyde, naringenin, kaempferol, and aromadendrin (Chacko et al., 2000; George et al., 2016). Verma et al. (2014) found that *D. arayalpathra* root volatile oil contains 2-hydroxy-4-methoxybenzaldehyde (96.8%) as the major constituent. Thangam et al. (2019) isolated 2-hydoxy 4-methylbenzaldehyde from fresh root bark.

22.3 PHARMACOLOGICAL STUDIES

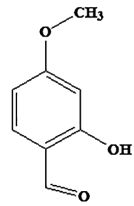
D. arayalpathra showed wide range of pharmacological properties and are discussed in subsections.

22.3.1 ANTIOXIDANT ACTIVITY

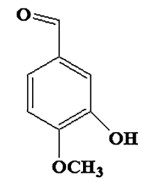
Total antioxidant activity of methanolic extract was found to be 330 ± 1.56 µg/ml followed by its butanol (198 µg/ml), aqueous (137 µg/ml), ethyl acetate (53.8 µg/ml) and chloroform (21.8 µg/ml) fractions. Methanol extract showed strong reducing power (1.59 µg/ml) as compared to ascorbate (2.17 µg/ml). Free radical scavenging potential of methanolic extract was analyzed by DPPH (IC_{50} 42.6 µg/ml) and H_2O_2 scavenging (IC_{50} 160.5 µg/ml) methods (Zishan et al., 2017).



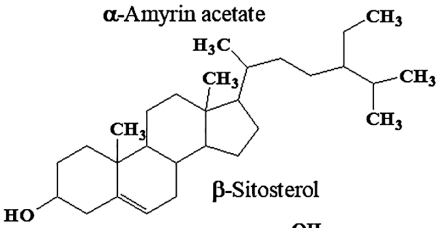
α-Amyrin acetate



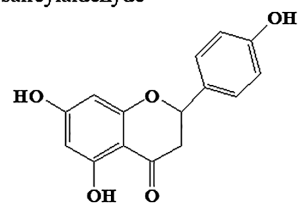
4-Methoxy salicylaldehyde



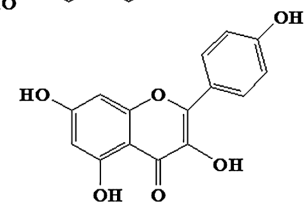
3-Hydroxy-p-anisaldehyde



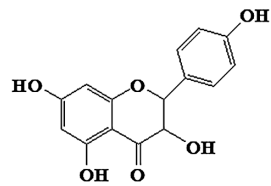
β-Sitosterol



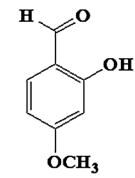
Naringenin



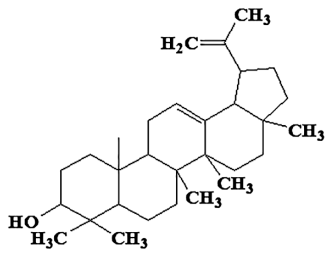
Kaempferol



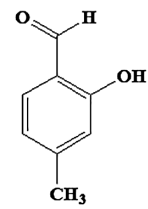
Aromadendrin



2-Hydroxy-4-methoxybenzaldehyde



Magnificol



2-Hydroxy-4-methyl benzaldehyde

22.3.2 IMMUNOMODULATORY AND ANTICANCER ACTIVITIES

Immunomodulatory and anticancer activities of *D. arayalpathra* was evaluated by Subramoniam et al. (1996). The root suspension at a dose of 500 mg/kg elicited an increase in humoral antibody titer and antibody secreting spleen cells indicating immunomodulatory effect mice. The extract also enhanced sheep RBC-induced delayed hypersensitivity reaction and increased blood granulocytes and peritoneal macrophages in mice. Anticancer potential of *D. arayalpathra* was evident from its protective effect against Ehrlisch

ascitic carcinoma cell growth in mice. Thangam et al. (2019) found that the 2-hydroxy 4-methylbenzaldehyde isolated from the fresh root bark of *D. arayalpathra* induces apoptosis in MDA-MB-231 breast cancer cells.

22.3.3 GASTROPROTECTIVE ACTIVITY

Gastroprotective effect of alcohol extract of *D. arayalpathra* roots in Wistar rats was evaluated by Shine et al. (2007). *D. arayalpathra* extract (250 mg/kg) significantly decreased the pepsin secretion and gastric juice volume, and decreased acid output (500 mg/kg) in pylorus ligated rats.

22.3.4 ANTI-VENOMOUS ACTIVITY

Alam et al. (2016) reported 2-hydroxy-4-methoxybenzaldehyde isolated from *D. arayalpathra* root extract showed good activity against viper and cobra envenomations.

22.3.5 ANTIMICROBIAL ACTIVITY

Raveesha and Ashalatha (2017) found that the aqueous and methanolic leaf extracts of *D. arayalpathra* showed maximum antibacterial activity against *Klebsiella pneumoniae*, whereas ethanolic and petroleum ether extracts of the callus showed maximum inhibition against *Escherichia coli* and *Bacillus subtilis*.

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KEYWORDS

- **anti-venomous activity**
- ***Decalepis arayalpathra***
- **Ehrlisch ascitic carcinoma cell growth**
- **gastroprotective effect**
- **immunomodulatory effect**
- **α-amyrin acetate**

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CHAPTER 23

Chemical Constituents and Biological Activities of *Diospyros vera* (Lour.) Chev.

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23.1 INTRODUCTION

Diospyros vera (Lour.) Chev. [Syn. *D. ferrea* (Willd.) Bakh.; *Maba buxifolia* (Rottb.) Pers.] is an evergreen bushy shrub found in dry deciduous forests. The plant is distributed in India, Sri Lanka, Myanmar, Malaysia, Indonesia, Singapore, Japan, North Australia and Africa. The plant is commonly called Philippine Ebony, Persimmon, and is known as *Uti*, *Yerruti*, *Chinna-ullingi* in Telugu, and *Tendu* in Hindi. Ethnobotanically the leaf juice is used to strengthen the liver (Swamynathan and Ramamoorthy, 2011). The genus *Diospyros* is one of the most important sources of bioactive compounds (1,4-naphthoquinones, known for the anticancer activity) (Nematollah et al., 2012). Sharma (2017) carried out a brief review on the genus *Diospyros* for its rich napthoquinones. The plant is an important ingredient of "*Jeevaprada YevvanaKashayam,*" an Ethnomedicinal syrup possessing free radical scavenging activity (Sripriya and Chandra, 2020).

Plants are evergreen, bushy shrubs; branchlets glabrous, bark gray to black. Leaves obovate-spathulate or elliptic. Flowers white or yellow,

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3-merous; male flowers in short cymes; female 10–13, together. Sepals and petals 3 each, stamens 6, ovary 3-locular; single ovule per locule. Berries globose, orange when ripe.

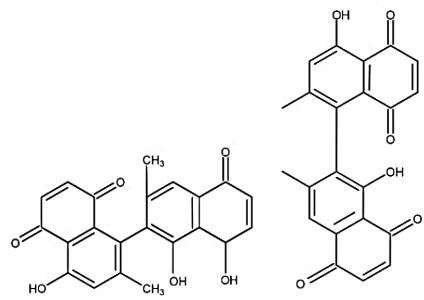
23.2 PHYTOCHEMISTRY

Chemical studies on a number of species of *Diospyros* have revealed that the stems and leaves of this genus have been reported to contain triterpenoids (Bhakuni et al., 1971). Tezuka et al. (1973) isolated 8-Hydroxyisodiospyrin ($C_{22}H_{14}O_7$) and Isodiospyrin ($C_{22}H_{14}O_6$) from root bark of *Diospyros vera* (syn.: *Diospyros ferrea*). Kuo et al. (1997) characterized lupeol, a cytotoxic compound from the fruit of *Diospyros vera.* The entire plant of *Diospyros vera* contains polyphenolic compounds, triterpenes, lupeol, scopoletin, betulin, β-sitosterol, stigmatosterol, diospyrin, isodiospyrin, benzopyrones, steroids, ursolic acid, and naphthalene-based aromatic hydrocarbons. These metabolites can be used as chemical markers for taxonomic studies (Mallavadhani, 1998). Preliminary phytochemical analysis of root of *Diospyros vera* using various solvents like hexane, chloroform, methanol, ethanol, and water showed alkaloids, cardiac glycosides, coumarins, terpenoids, phytosterols, anthrquinones, tannins, and saponins (Vijayalakshmi and Ravindran, 2012a). The ethanolic root extract of *D. vera* showed the presence of gallic acid with different range of Rf from 0.38 to 0.74. Gallic acid with the Rf value 0.46, 0.47 was reported in *Diospyros vera* (Vijayalakshmi and Ravindran, 2012b).

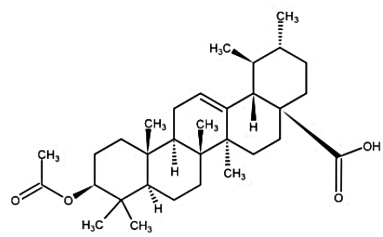
Gold nanoparticles (70–90 nm sized) were synthesized from *Diospyros vera* and were confirmed by SEM, UV, and FTRI analysis (Ramesh and Armash, 2015). Reddy et al. (2015a) investigated the presence of various phytochemicals from hexane, ethylacetate, and methanol extracts of *Diospyros vera* (Syn.: *Maba buxifolia*) stem. The three different extracts from stem revealed the presence of alkaloids, phlobatannins, tannins, glycosides, flavonoids, phenols, saponins, and terpenoids. Phytochemical analysis of *D. vera* leaf showed the presence of alkaloids, phlobatannins, tannins, glycosides, flavonoids, phenols, saponins, and triterpenoids (Jeevaprada et al., 2015). GC MS study of hexane, ethylaceatate, and methanolic stem extract showed 37 phytochemical compounds of which some are cetene, phorbol, thunbergeol, pregnenolene, androstenediol, betulin, squalene, fenretinidine, campseterol, lupeol, gitoxigenin, friedelan-3-one, etc. (Reddy et al., 2015b).

Rajesh et al. (2017) synthesized silver nanoparticles using *Diospyros vera* leaves. The structural details of the synthesized silver nanoparticles

were elucidated using X-ray diffraction method (XRD), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM) and Energy dispersive X-ray analysis (EDAX). Synthesized nanoparticles exhibited antioxidant activity. In GC-MS chromatogram of hexane extract, out of the seven peaks detected six were siloxane peaks representing hydrocarbons and one represents alkylated phenolic group. The GC-MS chromatogram of ethylaceate extract revealed 16 different peaks representing significant compounds such as phytol, squalene, tocopherol, α-amyrin, betulin, and friedelan besides other hydrocarbons. In methanolic extract galactitol, cetene, citronellol, tocopherol, pregnenolone, olen, and thunbergol are some of the important compounds identified (Jeevaprada et al., 2019).



8-hydroxyisodiospyrinIsodiospyrin



Ursolic Acid

23.3 BIOLOGICAL ACTIVITIES

23.3.1 ANTIOXIDANT ACTIVITY

The total antioxidant capacity of methanolic stem extract of *Diospyros vera* was evaluated by the phosphomolybdate assay method. The total antioxidant

capacity of the plant extract was expressed as the μg of ascorbic acid activity equivalent. The antioxidant activity of methanolic stem extract of *D. vera* was found to be 18.206 ± 0.25 (20 μg/ml), 37.1802 ± 0.56 (40 μg/ml), 54.2039 ± 1.0 (80 μg/ml) and 89.3405 ± 1.67 (160 μg/ml), respectively (Reddy et al., 2015c). Anand et al. (2018) evaluated the *in vitro* antioxidant activities of *D. ferrea* fruit extracts using different solvents by different antioxidant assays such as DPPH, RPA, SO, NO, HO, H_2O_2 and FRAP. Fruit extract showed 83.6% (DPPH), 1.89% (RPA), 82.9% (SO), 73.9% (NO), 81.4% (HO), 1.46% (H_2O_2) and 10.98% (FRAP) scavenging activity.

23.3.2 ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES

Ramana et al. (2010) studied root extracts of *Diospyros vera* for anti-inflammatory and analgesic activities. The extract showed 37% reduction in inflammation when compared with standard ibuprofen and exhibited significant analgesic activity. The chloroform and methanolic extracts of the leaves of *Diospyros vera* (100–300 mg/Kg) were tested for its anti-inflammatory and analgesic activities using carrageenan induced rat paw edema method and Tail flick method, respectively. The extracts showed 37% reduction in inflammation and significant analgesic activity (Rani and Ramana, 2011). The methanolic extract of *D. vera* was evaluated for anti-inflammatory activity by rat paw edema method. The extract at doses 200 and 400 mg/Kg showed maximum inhibition of paw volume by 1.631 ± 0.248 and 1.390 ± 0.226 ml, respectively at 240 min. Biochemical parameters like acid phosphatase and alakaline phophatase were estimated. Methanolic extract of the stem at 200 and 400 mg/Kg significantly reduced the raised levels of acid phosphatase. The level of serum alkaline phosphatase (ALP) was raised and this increase was normalized at 200 and 400 mg/Kg [2.170 ± 0.331 IU/L] [1.863 ± 0.143 IU/L] (Reddy and Ammani, 2015). Silver nanoparticles synthesized using *Diospyros* leaves were tested for anti-inflammatory activity by albumin denaturation assay. From the study, it was observed that maximum inhibition was found to be 65.21% at a concentration of 100 μg/mL and its IC_{50} was determined (6.67 μg/ml) (Rajesh et al., 2017).

23.3.3 ANTIDIABETIC ACTIVITY

Jeevaprada et al. (2017) evaluated the antidiabetic activity of methanolic leaf extract of *Diospyros vera* in streptozotocin (STZ) induced diabetic

rats for 21 days. The leaf extracts showed beneficial effect on parameters like blood glucose, serum lipid profile, serum protein, serum urea, uric acid, creatinine, glycosylated hemoglobin, liver glycogen, liver antioxidant enzymes and serum AST and ALT levels. Chronic treatment with methanolic extract of *Diospyros vera* leaf reduced blood glucose level throughout the experimental period in duration dependent manner, indicating its anti-hyperglycemic activity. Cholesterol and triglyceride levels of serum were near to normal in treated rats. A sharp rise in the serum AST and ALT levels was recorded. A significant decrease in the activity of antioxidant enzymes viz., catalase (CAT) and lipid peroxidase was observed in the blood serum. However, there was a significant increase in liver glycogen in rats treated with different doses of plant extracts. The leaf extract at high dose (400 mg/kg) exhibited significant anti-hyperglycemic activity than at low dose (200 mg/kg) in diabetic rats.

23.3.4 FIBRINOLYTIC ACTIVITY

Investigation of the thrombolytic activity of *D. vera* stem extract was carried out using a simple and rapid *in vitro* clot lysis model using urokinase as a standard reference. The results indicated clearly that concentrations of stem extract enhanced maximum (24.3%) of clot lysis (Reddy et al., 2015c).

23.3.5 ANTIMICROBIAL ACTIVITY

Diospryos vera derived gold nanoparticles were tested against the human pathogens such as *Bacillus cereus*, *Klebsiella pneumoniae*, *Candida albicans* and *Microsporum gypseum* using agar disc diffusion method. Plant derived gold particles were most effective against, *Klebsiella pneumoniae* while moderate effect was noticed with *Bacillus cereus*. Regarding antifungal activity, gold particles were more effective against *Microsporum gypseum* whereas average effect was observed in *Candida albicans* (Ramesh and Armash, 2015). Silver nanoparticles synthesized using *Diospyros vera* leaves were tested for antimicrobial activity by agar well diffusion method. The nanoparticles showed good antimicrobial activity against *Staphylococcus aureus, Micrococcus luteus, Escherichia coli, Klebsiella pneumoniae, Aspergillus flavus,* and *Aspergillus fumigatus* (Rajesh et al., 2017).

23.3.6 ANTI-CANCEROUS ACTIVITY

Hazra et al. (1984) reported the anti-tumor activity of bark extract of *D. vera*. and its active principle diospyrin-1 against Ehrlich ascites carcinoma (EAC) in Swiss Albino mice. The cytotoxic effect of the AuNPs was examined on human cell lines (HeLa cells) for 24 h and 48 h with a sample concentration of 0.1–50 µL. The AuNPs inhibited the growth of the cancer cells significantly, in a dose and duration-dependent manner. In Au NPS, the 50 µL sample is enough to control cancerous cells. Silver nanoparticles from leaf of *Diospyros vera* are used to study anti-cancerous activity in MCF-7 and HepG2 cell lines (Rajesh et al., 2017). The cytotoxicity effect is very high in AuNPs against HeLa cell lines (Ramesh and Armash, 2015).

KEYWORDS

- ***Diospyros vera***
- **Ehrlich ascites carcinoma**
- **energy dispersive x-ray analysis**
- **Fourier transform infrared spectroscopy**
- **scanning electron microscopy**
- **silver nanoparticles**
- **X-ray diffraction method**

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CHAPTER 24

Traditional Uses, Bioconstituents, and Pharmacological Aspects of Autumn Olive (*Elaeagnus umbellata* Thunb.)

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24.1 INTRODUCTION

Elaeagnus umbellata Thunb. belongs to the family Elaeagnaceae. *Elaeagnus crispa* Thunb., *Elaeagnus padifolia* K.Koch, *Elaeagnus parvifolia* Wall. ex Royle, *Elaeagnus praematura* (Koidz.) Araki are the synonyms of this species (www.theplantlist.org). The vernacular names of the plant are Spreading oleaster, Autumn olive, Japanese silverberry, Autumn elaeagnus, Umbellata oleaster, Kankal, Guenlee, Giwain, etc. (www.flowersofindia.net).

It is a deciduous shrub and grows up to 3.5 meters tall, branches dense crown with sharp thorns. Leaves alternate, 4–10 cm long, 2–4 cm wide, margins wavy, elliptic-oblong to oblong-lanceolate; young leaves covered with small silvery scales and greener during summer. Flowers in bunches, fragrant, 8–9 mm inches length, 7 mm diameter with four lobes. Fruit are small elliptic-ovoid drupe, 8–9 mm long; unripe fruit silvery-scaled and

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yellow, turns to red with brown or silver dots when ripe, pulpy, and sweet. Autumn Olive is native to India, Tibet, China, Korea, Pakistan, Afghanistan, Nepal, Japan, and Southern Europe regions. It is common along the dry exposed places of 1,000–3,300 meters elevations in Himalayan region (POWO, 2019).

Due to its ornamental importance, drought tolerance, environmental adaptability and its compact nature, it is commonly grown in Himalayan urban areas as a hedge. In Pakistan and Italy, it is mainly used for fuel wood, fodder, and ornamental purposes. Plant fruits are used to prepare jams, preservatives, juice, and other food stuffs. In Indian traditional medicine, the flowers of the plant are used against heart and respiratory ailments; whereas, the seed oil is used for the treatment of cough and pulmonary infections. The decoction and tonic prepared from leaves are used to treat bowel disorders in China and Japan. Fruits of the plant are very good medicine for diarrhea, hepatitis, bone fractures and injuries (Gamba et al., 2020; Iannuzzi et al., 2020).

24.2 BIOACTIVES

The volatile compounds were isolated from *E. umbellata* through simultaneous steam distillation (SD) as well as purge and trap process. Volatiles were further analyzed through GC-MS technique (Potter, 1995). A total 131 peaks were detected and out of these, structures of 93 compounds were characterized. The major compounds were eugenol, (E)-2-nonenal, phenylacetaldehyde, palmitic acid, 4-methyl phenol and C_{14} to C_{20} fatty acid methyl esters. The most abundant compounds were (E)-2-hexenal, (Z)-3-hexenyl acetate, 4-methyl anisole, 4-methyl phenol and 4-methoy anisole. Asghar and Rehman (2012) analyzed methanol extract of whole plant and isolated a new isoflavone compound 3-(hydroxymethyl)-4-methoxyphenol, 5,7-dihydroxy-3(2-hydroxyphenyl)-4H-chromen-4-one and stigmasterol. The methanol extract of the whole plant was subjected to column chromatography using petroleum ether (PE) and dichloromethane as eluting solvents (Minhas et al., 2013b). Further, fractionations of the extract yielded six compounds such as 7-hydroxy-chromen-2-one; 7,8-dihyroxy-chromen-2-one; 3-(2,2,3,4,5-pentahydroxy-hexyloxy)-chromen-2-one; an anthraquinone, β-sitosterol glucopyranoside and lupeol. Nazir et al. (2018) quantified phenolic compounds from 80% methanol, chloroform, and ethyl acetate (EA) extracts through HPLC-UV method. Authors could identify the presence of 12 phenolic compounds and among them, epigallocatechin gallate showed higher concentration (58.3 μg/mL) followed by pyrogallol, rutin, catechin

hydrate and chlorogenic acid (52.1, 45.2, 39.8, and 23.1 μg/mL, respectively). Iannuzzi et al. (2020) extracted plant fruits with methanol and it was further partitioned with organic and aqueous solvents (EA, n-butanol, and water). The flash chromatography, sephadex LH-20 and RP-HPLC analyzes of EA and n-butanol extracts yielded many compounds such as isorhamnetin 3-O-α-L-xylopyranosyl-(1→2)-β-D-glucopyranoside, 2-hydroxynaringenin 7-O-β-D-glucopyranoside, tiliroside, kaempferol 3-O-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside, kaempferol 3-O-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside, kaempferol 3-O-β-D-glucopyranoside, quercetin 3-O-α-L-xylopyranosyl-(1→2)-β-D-galactopyranoside, 1-O-(trans-sinapoyl)-β-D-glucopyranoside and quercetin 3-O-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside.

Gamba et al. (2020) carried out the extraction of fruits using organic solvents and the major fractions found rich in polyphenols (65.56%), monoterpenes (27.40%) and vitamin C (7.04%). In polyphenol fraction, majority of the compounds were represented by anthocyanins (71.9%). A total of 23 bioactive compounds were reported from the phytochemical fingerprint of the plant. Several compounds such as limonene (34.34), phellandrene (8.33), sabinene (26.16), γ-terpinene (28.90), terpinolene (15.59), ascorbic acid (5.66), dehydroascorbic acid (23.46), caffeic acid (0.78), chlorogenic acid (10.93), coumaric acid (5.82), ferulic acid (1.32), hyperoside (7.20), isoquercitrin (0.10), quercetin (8.95), quercitrin (0.15), rutin (0.76), ellagic acid (5.50), gallic acid (0.16), catechin (1.62), epicatechin (3.38), castalagin (5.00), vescalagin (24.54) and anthocyanins (194.99) have been reported as mg/100 g fresh weight.

Paudel et al. (2020) extracted leaves and twigs of the plant using methanol solvent and further fractionation of the extract yielded 12 compounds. It included two flavonoid coumaroyl glycosides [kaempferol-3-β-D-(6-O-trans-p-coumaroyl) glucopyranoside and kaempferol-3-β-D-(6-O-cis-p-coumaroyl) glucopyranoside], two phenolic compounds (vanillin and trans-cinnamic acid), one coniferyl alcohol derivative [2-{4-(3-hydroxy-1-propenyl)-2-methoxy-phenoxy}-1,3-propanediol], one monoterpene [(+)-menthiafolic acid], two pairs of enantiomeric neolignans [(±)-dehydrodiconiferyl alcohol and (±)-dihydrodehydrodiconiferyl alcohol] and a pair of enantiomeric sesquineolignans [(±)-jatrointelignan B]. Recently, Nazir et al. (2021) carried out a GC-MS analysis of essential oil from fruits. In the study, major identified compounds were (–)caryophyllene oxide (39.4%); -(–)

caryophyllene (31.2%); humulene epoxide (25.4%); coumarin, 7-methoxy (15.4%) reported (Figure 24.1).

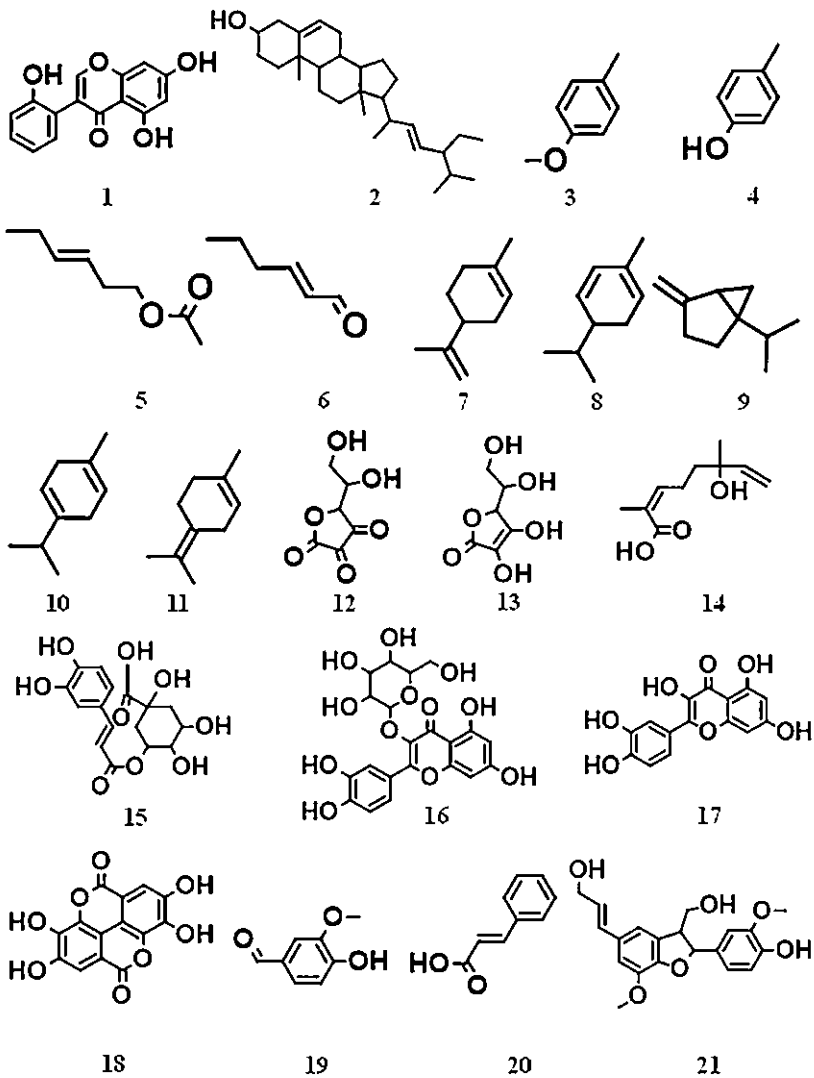


FIGURE 24.1 Structures of 5,7-dihydroxy-3(2-hydroxyphenyl-4H-chromen-4-one (1); stigmasterol (2); 4-methyl anisole (3); 4-methyl phenol (4); (Z)-3-hexenyl acetate (5); (E)-2-hexenal (6); limonene (7); phellandrene (8); sabinene (9); γ-terpinene (10); terpinolene (11); dehydroascorbic acid (12); ascorbic acid (13); (+)-menthiafolic acid (14); chlorogenic acid (15); hyperoside (16); quercetin (17); ellagic acid (18); vanillin (19); trans-cinnamic acid (20); and (±)-dehydrodiconiferyl alcohol (21).

24.3 PHARMACOLOGY

24.3.1 ANTIOXIDANT ACTIVITY

Khattak et al. (2012) studied the antioxidant activity of aqueous, methanol, and acetone extracts of *E. umbellata* fruits. The highest extraction yield was found in methanol extract (24.1%), followed by aqueous and acetone (17.5 and 15.3%, respectively). Further, methanol extract also showed the highest DPPH radical scavenging activity (10.7, 26.7, 49.0, 69.3, 84.9, and 90.2% inhibition) at 20, 40, 60, 80, 100, and 120 µg/mL concentrations, respectively. The activity was found to be dose-dependent. The lowest EC_{50} values for methanol and acetone extracts were 97.3 and 188.0 µg/mL, respectively. Iannuzzi et al. (2020) isolated five new compounds (four triterpenoid saponins and a sesquiterpenoid glucoside) and nine known phenolic compounds from the fruits. These compounds were evaluated for *in vitro* antioxidant assay in human gingival fibroblasts. Interestingly, among all the compounds isolated, kaempferol 3-O-β-D-glucopyranosyl-(1→2)-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside declined the intracellular reactive oxygen species (ROS) production and significantly counteracted the reduction of human gingival fibroblast cell numbers influenced by hydrogen peroxide (H_2O_2) and it promoted the proliferation of live cells. Recently, Nazir et al. (2021) found noteworthy free radical scavenging activity of fruit essential oil, which was comparable to ascorbic acid. The higher potentiality was recorded against DPPH and ABTS (85.24 ± 0.63 and 88.30 ± 0.81 µg/mL, respectively) at 1,000 µg/mL concentration with IC_{50} of 70 and 105 µg/mL, respectively. Whereas, standard ascorbic acid showed 91.56 ± 0.35 and 92.63 ± 0.99% inhibition for DPPH and ABTS radicals at 1,000 µg/mL with IC_{50} values of 32 and 29 µg/mL, respectively.

24.3.2 ANTI-PROLIFERATIVE EFFECTS

Kim et al. (2016) evaluated anti-proliferative efficacy of leaf, stem, and fruit ethanol extracts. The leaf extract showed the highest activity against HepG2 cells measured through MTT and lactate dehydrogenase methods. However, the extract did not show any significant effects on Chang liver cells.

24.3.3 MELANOGENESIS INHIBITORY ACTION

Recently, melanogenesis inhibitory effects of isolated fractions were tested against B16-F10 melanoma cells (Lee et al., 2021). Authors evaluated the

effects of fractions on tyrosinase and melanogenesis B16-F10 melanoma cells induced with α-melanocyte-stimulating hormone. Doses found to be noncytotoxic at 12.5–50 µg/mL and fractions used in the study effectively inhibited the process of melanogenesis as well as tyrosinase activity. It down-regulated the protein expressions of melanogenesis and its pathways by suppressing the phosphorylation of ERK and CREB. It is of interest to note that the anti-melanogenesis effect was noted at 50 µg/mL concentration of fractions and the activity was significantly higher than those of the extract. Researchers also found that the fractions exhibited strong free radical scavenging activity and blocked the melanogenesis proteins (tyrosinase, TRP-1 and TRP-2) regulating MITF. Hence, it could be used as a valuable natural inhibitor of melanogenesis. Notably, extract, and fractions (50 µg/mL) inhibited melanin synthesis in α-MSH-stimulated B16-F10 cells. These findings confirmed the use of *E. umbellata* as a natural therapeutic mediator in the treatment of skin diseases and as skin-whitening agents in cosmetics industries (Lee et al., 2021).

Park et al. (2019) investigated the efficacy of hydro-ethanolic extract of *E. umbellata* leaves on skin health. The extract decreased the production of intracellular melanin significantly by 33.0% at 100 µg/mL dose, when compared to untreated B16-F0 cells. It also down regulated tyrosinase activity in stimulated B16-F0 cells through 47.8% inhibition at 100 µg/mL concentration. The extract significantly increased the production of type I procollagen in CCD-986sk cells up to 1.74-fold at 250 µg/mL, compared to UVB-irradiated control cells. It was also found that the extract also inhibited the discharge of MMP-1 to the media from UVB-irradiated CCD-986sk cells at 10–500 µg/mL. The efficacious activity of the extract indicated its use in cosmetic industries due to its whitening and anti-wrinkle effects.

24.3.4 ANTIMICROBIAL ACTIVITIES

PE extract of the leaves exhibited potential antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and *Bordetella bronchisiptica* with 19.35 ± 0.15, 19.22 ± 0.11, and 6.93 ± 0.06 mm inhibition zones, respectively. Similarly, the chloroform extract revealed the highest activity against *E. coli* (20.56 ± 0.23 mm), *Pseudomonas syringae* (17.16 ± 0.16 mm), *Bordetella bronchisiptica* (16.30 ± 0.16 mm), *Bacillus subtilis* (16.22 ± 0.08 mm), *Pseudomonas aeruginosa* (15.00 ± 0.00 mm) and *S. aureus* (10.00 ± 0.00 mm) (Minhas et al., 2013a).

24.3.5 ANTIPLASMODIAL ACTIVITY

Minhas et al. (2013b) studied antiplasmodial activity of six compounds isolated from whole plant, such as: 7-hydroxy-chromen-2-one (1); 7,8-dihyroxy-chromen-2-one (2); 3-(2,2,3,4,5-pentahydroxy-hexyloxy)-chromen-2-one (3); and an anthraquinone (4); together with β-sitosterol glucopyranoside (5); and lupeol (6) against *Plasmodium falciparum* isolates (NF54 and R). Compounds 1 to 4 at 3 µM concentration showed partial suppression of *P. falciparum* NF54. The potent antiplasmodial activity was observed for compound 3 when compared to untreated controls on day 4 after the treatment. *P. falciparum* strain NF54 treated with different concentrations (2 to 8 µM) of 7-β-D-glucosyl coumarin (compound 3) resulted in a partial inhibitory effect at 4 µM and found stronger than 8 µM.

24.3.6 ANTIDIABETIC POTENTIAL

Nazir et al. (2018) evaluated the antidiabetic activity of 80% methanol extract and its fractions (n-hexane, chloroform, EA, and n-butanol) from *E. umbellata* fruits. The enzyme inhibitory potential of the extract and fractions against α-amylase and α-glucosidase enzymes were determined. *In vivo* STZ-induced type 2 antidiabetic activity was carried out using Sprague Dawley adult rats. It was reported that the EA and chloroform fractions were comparatively active against α-amylase and α-glucosidase enzymes (IC_{50} 200 and 58 µg/L; 140 and 60 µg/mL, respectively). Moreover, these two fractions found more effective in the management of hyperglycemia and caused significant reduction in glucose level when compared to non-treated group. Recently, Nazir et al. (2021) extracted essential oil from the fruit using hydro-distillation process and identified total 68 compounds through GC-MS technique. The antidiabetic potentiality of crude essential oil was proved against α-glucosidase and α-amylase with IC_{50} values of 120 and 110 µg/mL as compared to the standard acarbose (IC_{50} 28 and 30 µg/mL, respectively).

24.3.7 NEUROPROTECTIVE ACTIVITY

Nazir et al. (2020) assessed the neuroprotective and anti-amnesic effects of crude extracts as well as isolated compounds from fruits on the central nervous system (CNS). Major phytochemicals (phenolics and flavonoids)

present in methanolic extract were qualitatively determined. Extract and fractions were subjected to investigate cholinesterase (AChE and BChE) inhibitory activity. Among different fractions, chloroform, and EA extracts showed the highest inhibitory activities against AChE (87 ± 1.2 and 84 ± 1.0%) with IC_{50} values of 33 and 55 µg/mL, respectively. Similarly, both the fractions revealed the highest percent inhibition (86 ± 0.3 and 82 ± 0.5%) of BChE with IC_{50} values of 35 and 58 µg/mL, respectively. Methanolic extract and subsequent fractions exhibited a dose-dependent inhibition of cholinesterase enzymes. Donepezil, a positive control used in the study, showed 92 ± 0.3% BChE inhibition with IC_{50} of 28 µg/mL.

24.3.8 CARDIOVASCULAR ACTIVITY

Qayyum et al. (2019) explored the medicinal applications of *E. umbellata* methanolic fruit extract and its fractions (EA and n-hexane) against cardiovascular diseases. The EA fraction showed significant antihypertensive activity at the dose of 300 mg/kg and caused a decrease in blood pressure to 59 ± 1.00 mm Hg. Further, EA fraction caused a vasorelaxant effect with an EC_{50} value of 0.328 mg/mL in intact endothelium. It has also been found that the EA and n-hexane fractions from 0.01–10.00 mg/mL doses suppressed the transient contractile responses in experimental animals.

24.3.9 CALCIUM ENTRY BLOCKING ACTIVITY

Recently, Rafique et al. (2021) explored the pharmacological effects of *E. umbellata* fruit methanol extract and its fractions in gut disorders through castor oil-induced diarrhea in rat models. The study revealed that the crude methanol extract and positive standard verapamil reduced the wetness of fecal droppings and provided 71.9 and 80.9% protection. In the rabbit jejunum measurements, crude extract caused inhibition of high potassium ion-induced contractions, with EC_{50} of 3.4 mg/mL. The treatment of n-hexane (0.1–1 mg/mL), chloroform (1–5 mg/mL), and EA (0.1–1 mg/mL) fractions caused a rightward shift in the calcium ion concentration-response curves. Interestingly, the aqueous fraction did not cause any spontaneous and high potassium ion-induced contractions.

KEYWORDS

- **antihypertensive activity**
- ***Autumn olive***
- **bioactives**
- **cholinesterase enzymes**
- ***Elaeagnus umbellata***
- ***Escherichia coli***
- **pharmacological effects**

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CHAPTER 25

Bioactive Constituents and Pharmacological Properties of *Ephedra gerardiana* Wall. ex Stapf and *Ephedra intermedia* Schrenk & C.A. Mey.

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25.1 INTRODUCTION

Ephedra gerardiana Wall. ex Klotzsch & Garcke [Synonym: *E. gerardiana* var. *wallichii* Stapf] and *Ephedra intermedia* Schrenk & C. A. Mey. [Synonyms: *E. glauca* Regel, *E. ferganensis* V.A.Nikitin, *E. intermedia* var. *glauca* (Regel) Stapf, *E. heterosperma* V.A.Nikitin, *E. persica* (Stapf) V.A.Nikitin, *E. microsperma* V.A.Nikitin, *E. tibetica* (Stapf) V.A.Nikitin, *E. tesquorum* V.A.Nikitin, and *E. valida* V.A.Nikitin] belong to the family Ephedraceae.

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E. gerardiana is native to Afghanistan, Pakistan, Nepal, West Himalaya, East Himalaya, Qinghai, Tibet, Tuva, and Xinjiang. Whereas, nativity of *E. intermedia* is Afghanistan, Kazakhstan, Kirgizstan, Pakistan, Tadzhikistan, Uzbekistan, Turkmenistan, Altay, Iran, Mongolia, Transcaucasus, West Siberia, Tibet, Xinjiang, and West Himalaya (http://www.plantsoftheworldonline.org). The vernacular names of *E. gerardiana* are Gerard jointfir, Somlata, Soma, Ain, Khanta, Chhepat, Buchchur, etc. Whereas, *E. intermedia* is commonly called Central-Asian joint fir and Zhong ma huang in China (www.flowersofindia.net).

E. gerardiana is a rigid tufted shrub, grows up to 1–2 feet high. Stem erect, stout, slender, densely clustered, green, scabridulous, jointed branches with 1–3 nodes. Leaves opposite, 2 to 3 mm width, connate. Male cones solitary or 2 to 3 in numbers, ovate, 6–8 mm size, each cone having 4–8 flowers, with fused filaments and rounded bracts. Female cones are usually solitary. Fruit ovoid, 7–10 mm size with seeds enclosed in fleshy red succulent bracts (POWO, 2019; www.flowersofindia.net).

E. intermedia is an evergreen shrub, grows up to 1 meter tall, densely branched, erect or spreading, sometimes creeping stem produces green, single, and erect primary branches. Branchlets often powdery with yellow or bluish green, with straight or slightly bent internodes. Leaves in whorls of 3, fused, forming a cone-like structure. Male cones often sessile, usually clustered at nodes; bracts in whorls or 3 to 4 pairs; anthers sessile or shortly stipitate. Fruit is a berry, ovoid, red, and fleshy at maturity. Seeds 2 to 3, ovoid or elongate-ovoid in shape, concealed in bracts (POWO, 2019; www.flowersofindia.net).

In Indian folk medicine, *E. gerardiana* has been widely used since the Vedic period as a substitute for psychoactive drink 'soma.' It is also reported as nasal decongestant, to treat asthma, hay fever, rheumatism, syphilis, rashes of allergic origin, cardiac problems, bronchitis, along with various other lung related disorders (Abourashed et al., 2003; Singh et al., 2013; Chaudhary et al., 2020; www.flowersofindia.net). The rural communities of the cold arid desert region of Ladakh, India have more or less dependent on this plant for ornamental, medicinal, fodder, and fuel purposes (Akbar et al., 2011). The local communities of Northern areas of Pakistan, use whole plant, root, and stem in treating respiratory tract infections, joint pain, bone fractures, rheumatism, syphilis, and heart diseases (Uttra and Alamgeer, 2021).

Similarly, different parts of *E. intermedia* have been widely used to treat asthma as it helps to reduce the lung swelling during heart attacks (www.flowersofindia.net). The women folk healers of Khuzdar and Kalat province of Balochistan, use decoction of whole plant to treat typhoid, asthma, and

chest infection. Mature fruits of the plant are also reported to prepare the decoction and utilized medicinally as a stimulant, diaphoretic, anti-asthmatic, and to treat tuberculosis (Bangulzai et al., 2017; Gul et al., 2017). In Iran, the local people make poultice from the plant to cure inflammations due to injuries in cattle as well as in humans (Ni et al., 2019). Zhang et al. (2018) and Gonzalez-Juarez et al. (2020) reviewed the phytochemistry and pharmacology of different species of *Ephedra*.

25.2 BIOACTIVES

E. gerardiana is known for the production of one of the rare and clinically important drug ephedrine (Akbar et al., 2011). Chemical constituents from *Ephedra* species is the research of interest from many decades due to the presence of ephedrine-type alkaloids and their pharmacological properties. Pharmacology and phytochemical studies of different *Ephedra* species confirmed the presence of the most common active compounds (–)-ephedrine and (+)-pseudoephedrine (Abourashed et al., 2003). The genus *Ephedra* has great bio-active potential and its active metabolites have been modified structurally to improve their activities and to design new bio-active molecules (Gonzalez-Juarez et al., 2020). The major bioactive compound in *Ephedra* is (–)-ephedrine, with 40–90% concentrations of the total alkaloid fraction, followed by (+)-pseudoephedrine. Along with these, other alkaloids such as (–)-norephedrine, (–)-methylephedrine, (+)-norpseudoephedrine and (+)-methylpseudoephedrine were also recorded. The total alkaloid content found more than 2%, which was species dependent (Bruneton 1995). Konno et al. (1979) isolated ephedroxane from the dried aerial parts of *E. intermedia*. Further, Cui et al. (1991) recorded the alkaloids such as norpseudoephedrine, norephedrine, ephedrine, pseudoephedrine, methylephedrine from *E. intermedia*. Whereas, the compounds norpseudoephedrine, norephedrine, ephedrine, pseudoephedrine, and methylephedrine traces of methylpseudophedrine have been isolated from *E. gerardiana*.

Ji et al. (1997) identified 127 volatile compounds from the stem of *E. sinica*, *E. intermedia* and *E. equisetina* using GC-MS, in which 1,4-cineole (12.80%) was recorded as a major compound from *E. intermedia*. Further, Ni et al. (2019) identified 21 compounds from essential oil of aerial parts of *E. intermedia* and out of which, 2-ethyl-pyrazine (67.37%), γ-elemene (9.21%), benzyl acetate (9.10%) and 2-methyl-butyl acetate (5.28%) were found to be the major compounds (Figure 25.1).

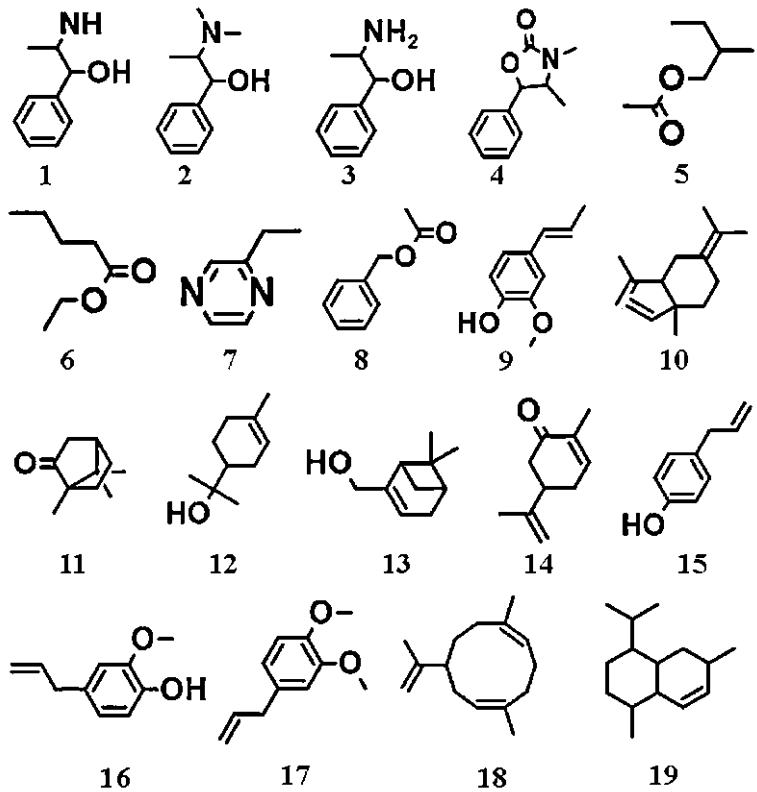


FIGURE 25.1 Structures of (–)-ephedrine (1); (–)-methylephedrine (2); (–)-norephedrine (3); ephedroxane (4); 2-methyl-butyl acetate (5); ethyl pentanoate (6); 2-ethyl-pyrazine (7); benzyl acetate (8); Z-isoeugenol (9); γ-elemene (10); camphor (11); α-terpineol (12); myrtenol (13); carvone (14); chavicol (15); eugenol (16); methyl eugenol (17); germacrene A (18); and cadinene (19).

25.3 PHARMACOLOGY

25.3.1 ANTIMICROBIAL ACTIVITY

Bangulzai et al. (2017) studied the antimicrobial activity of *E. intermedia* against some selected bacterial and fungal strains. The methanolic root extracts revealed the strongest antibacterial activity against *Staphylococcus aureus* (22, 18, and 14.7 mm zone of inhibition) at 20, 15, and 10 mg/mL. The lowest antibacterial activity was recorded (4, 2, and 1.4 mm zone of inhibition) in distilled water extract against *Bacillus subtilis* at 20, 15, and

10 mg/mL concentrations, respectively. As compared to root extracts, the extract from dried shoots showed comparatively lesser antibacterial activity against all the tested bacterial strains. Maximum antibacterial activity from shoot methanol extract was exhibited against *S. aureus* (19, 14.3, and 12 mm zone of inhibition). Similarly, the root methanol extract showed maximum antifungal activity against *Fusarium veriticilliodes* (21, 17, and 14 mm zone of inhibition) at 20, 15, and 10 mg/mL concentrations. Further, Ni et al. (2019) isolated the essential oil from aerial parts of *E. intermedia* and carried out the antimicrobial activity against some selected strians. The highest antimicrobial activity was found against *Enterococcus faecalis*, followed by *S. aureus*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. They have also recorded the minimum inhibition concentration (MIC) against the selected microorganisms *viz*. *S. aureus* (0.25 ± 0.00 mg/mL), *E. faecalis* (0.21 ± 0.07 mg/mL), *E. coli* (0.25 ± 0.00 mg/mL), *K. pneumoniae* (0.50 ± 0.00 mg/mL), *P. vulgaris* (0.33 ± 0.14 mg/mL) and *P. aeruginosa* (0.33 ± 0.14 mg/mL).

Khan et al. (2017) also determined the antibacterial potential of crude extracts and fractions of *E. gerardiana* using disc diffusion method. Amongst all, the zone of inhibition of chloroform and n-butanol fractions showed better responses against *B. atrophaeus* and *Bacillus subtilis* (13.3 ± 2.08 and 14.3 ± 1.53 mm; 14 ± 1 and 12 ± 1 mm, respectively). Similarly, ethyl acetate (EA) fraction also showed significant results against *K. pneumoniae* and *P. aeruginosa* (12.7 ± 1.53 and 13.7 ± 1.53 mm, respectively). In addition, aqueous fraction showed 13 ± 1 and 9 ± 1 mm zone of inhibitions against *B. atrophaeus* and *K. pneumoniae*, respectively. Crude methanolic extract showed 13.3 ± 1.53 mm inhibition against *B. atrophaeus*. Zone of inhibition against *B. atrophaeus* (12 ± 1 mm) and *K. pneumoniae* (12.3 ± 0.58 mm) were observed in n-hexane fraction. The EA fraction was most potent against all the tested organisms *viz. B. atrophaeus, K. pneumoniae, B. subtilis* and *P. aeruginosa* with 13 ± 1, 12.7 ± 1.53, 12.3 ± 2.08, and 10.3 ± 1 mm zone of inhibitions, respectively. However, the crude extracts and fractions failed to exhibit the antifungal activity against *Aspergillus niger* and *Aspergillus flavus.*

25.3.2 ANTI-ASTHMATIC ACTIVITY

Chaitanya et al. (2014) investigated the effects of *E. gerardiana* on airway resistance and airway inflammation in an ovalbumin (OVA) induced sensitized mouse model of asthma. Plant extract (100 and 200 mg/kg)

significantly reduced the total number of cells (2820 ± 34.84 and 2104 ± 12.81 per cu mm) and eosinophils (128.4 ± 3.95 and 105.4 ± 3.70 per cu mm) in broncheoalveolar lavage (BAL) during 21 to 23 days challenges and 1 to 20 days of sensitization. The treatment of extracts was also confirmed the reduction in peribroncheal, perivascular, and parenchymal inflammation using histopathology. Lung histology of the animals treated with plant extract confirmed the reduction in tissue edema, hypertrophy, infiltration, and airway lumen plugging. Further, it led to the decreased inflammation and broncoconstriction, resulted in normal lumen size.

25.3.3 ANTITUMOR AND CYTOTOXICITY ACTIVITY

The root extract of *E. gerardiana* showed significant brine shrimp cytotoxic activity (ED_{50} value of 523.8 ppm), followed by stem extract (ED_{50} value >1,000 ppm). Root extract at 1,000, 100, and 10 ppm concentrations inhibited 61.18, 35.29, and 9.41% tumor formations, respectively. Similarly, 1,000, 100, and 10 ppm of the stem extract inhibited 55.29, 35.29, and 23.53% tumor formations, respectively (Jamil et al., 2012).

25.3.4 ANTIPROLIFERATIVE ACTIVITY

The essential oil obtained from *E. intermedia* was tested for antiproliferative activity on human cervical carcinoma cells (HeLa), human prostate adenocarcinoma cells (LnCap cells) and human colon cancer cells (HCT116) (Ni et al., 2019). The oil exhibited a dose-related activity in all the tested cell lines and among all, the highest activity was obtained against HeLa (IC_{50} = 423.22 ± 8.243 μg/mL), followed by HCT116 (IC_{50} = 543.02 ± 5.63 μg/mL) and the least activity was observed in LnCap cell line (616.28 ± 6.22 μg/mL).

25.3.5 HEMOLYTIC ACTIVITY

Ni et al. (2019) analyzed the hemolytic activity of different concentrations of *E. intermedia* flower essential oil (0.005 to 2.5 mg/mL) in human blood. It was found that the oil exhibited almost unnoticeable hemolytic rates on hRBCs, ranged between 0.25% and 2.53%.

25.3.6 ANTI-ARTHRITIC ACTIVITY

Uttra and Alamgeer (2021) analyzed the anti-arthritic activity of aerial part of *E. gerardiana* hydro-ethanolic extract and its n-butanol, EA, and aqueous fractions (50–6,400 µg/mL) using *in vitro* (thermally induced bovine serum albumin (BSA) denaturation, egg albumin denaturation and membrane stabilizing assay) and *in vivo* (formaldehyde induced arthritis in rats) assays. The hydro-alcoholic extract and aqueous fraction at 6,400 µg/mL showed 32.19% and 28.99% egg albumin denaturation. Similarly, 6,400 µg/mL of hydro-ethanolic extract showed 99.1% BSA denaturation, followed by aqueous, n-butanol, and EA fractions (98.5, 92.1, and 85.7%, respectively). Membrane stabilizing assay confirmed the erythrocyte membrane protection capacity of hydro-ethanolic, aqueous, n-butanol, and EA fractions (6,400 µg/mL) against heat-induced lysis and hypotonic solutions with 9.3, 86.3, 67.1, and 47.0% respectively. *In vivo* assay showed decreased hind paw volume (79.1, 76.2, 65.0, and 54.0%) and paw diameter (75.0, 73.6, 61.0, and 50.9%) when treated with 200 mg/kg of hydro-ethanolic extract, aqueous, n-butanol, and EA fractions, respectively on 10th day.

25.3.7 ANTIOXIDANT ACTIVITY

Kumar et al. (2010) found promising antioxidant potential of *E. gerardiana* methanol extract with 13.30 + 0.6 µg/mL IC_{50}. Recently, Khan et al. (2017) investigated the antioxidant activity of *E. gerardiana* root and stem crude extracts and their respective fractions. Strong free radical scavenging activity was recorded by chloroform and EA fractions of root (IC_{50} 6.38 ± 1.59 and 2.96 ± 0.39 µg/mL, respectively), followed by n-hexane fraction, crude methanol extract and n-butanol fraction (21.49 ± 6.26, 14.94 ± 3.54, and 13.74 ± 2.71, respectively). The stem crude extract and its aqueous, EA, and n-butanol fractions showed strong free radical scavenging activities (IC_{50} 3.44 ± 0.69, 2.73 ± 0.84, and 2.69 ± 0.26 µg/mL), whereas chloroform and n-hexane fractions showed low antioxidant potential (IC_{50} 22.73 ± 6.92 and 13.92 ± 6.04 µg/mL, respectively).

KEYWORDS

- **anti-arthritic activity**
- **broncheoalveolar lavage**
- ***Ephedra gerardiana***
- ***Ephedra intermedia***
- **ephedrine**
- **human cervical carcinoma**
- **minimum inhibition concentration**

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CHAPTER 26

Biomolecules and Therapeutics of *Eriobotrya japonica* (Thunb.) Lindl.

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26.1 INTRODUCTION

Eriobotrya japonica (Thunb.) Lindl. [Syn.: *Crataegus bibas* Lour.; *Mespilus japonica* Thunb.; *Photinia japonica* (Thunb.) Franch. & Sav.] belongs to the family Rosaceae. It originated in southeastern China and was globally distributed to China, Spain, Japan, South Korea, India, Pakistan, Turkey, Israel, Egypt, Cyprus, Italy, France, Greece, Portugal, Madagascar, Syria, Australia, United States, Mexico, Brazil, Argentina, Armenia, Chile, and Tunisia (Zhou et al., 2007; Gong et al., 2015; Li et al., 2016). Commonly, it is called Loquat, Japanese plum tree or yellow plum tree (English), Beshmelah (Arabic), Loquate (German), Bibassier (French), Luju, and Biba (Chinese) (Gong et al., 2015; Alwash, 2017). China is the largest fruit producer with annual output of about 1 million tons, followed by Spain, Pakistan, and Turkey (40,000, 30,000, and 10,000–20,000 tons annually, respectively) (Li et al., 2016).

It is evergreen and naturally grows up to 10 m in height. In cultivated regions, it can grow up to 3–4 m in height, short trunk, rounded canopy, branched, velvety. Root system is superficial, 25–30 cm deep. Leaves simple, elliptic-lanceolate or oval-oblong, serrated margin, thick, rigid texture, 10 to 25 cm long, evergreen with upper surface is dark green and lower surface is

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white or rusty. Flower 2 cm in diameter, bunched with 3–10 white flowers, each flower 2 cm in diameter with 5 petals, before opening velvety texture, sweet fragrance. Fruit pommel type, fleshy, spherical to oval shaped, 3–5 cm in diameter. Peel velvety in texture, after maturity, yellow to orange or pink in color. Pulp juicy, firm, and fleshy, soft, white to orange in color, sweet to acidic flavor. Seeds 3–5 in number, brown color. Flowering in early winter or autumn and fruit ripening in early spring or late winter (Delucchi and Keller, 2010; Delfanian et al., 2015; Alwash, 2017).

It is a well-known medicinal plant in China and Japan. Different plant parts are sedative, diuretic, and also used in treatment of skin diseases, alleviated thirst, stomach, and lung illness, vomiting, wound, coughs diabetes, chronic bronchitis, cancers, ulcers, inflammation, dysmenorrhea, phlegm, antipyretic, asthma, headache, and lower back pain (Ito et al., 2000; Taniguchi et al., 2002; Koba et al., 2007; Alshaker et al., 2011; Fouedjou et al., 2016; Rajalakshmi et al., 2017). Several studies confirmed its health benefits in terms of bioactivities such as anti-inflammatory, antioxidant, hypolipidemic, hypoglycemic, antitumor, antimutagenic, antiviral, and cytotoxic (Baljinder et al., 2010).

26.2 BIOACTIVES

Seven triterpenes viz. oleanolic acid, ursolic acid, maslinic acid, 2α-hydoxyursolic acid, tormentic acid, 2α,19α-dihydroxy-3-oxo-urs-12-en-28-oic acid and hyptadienic acid along with mixture of 3-O-cis-p-coumaroyltormentic acid and 3-O-trans-p-coumaroyltormentic acid from the callus were identified (Taniguchi et al., 2002). Further, Ho et al. (2008) identified new bioactive triterpene, corosolic acid from leaves using HPLC. Kikuchi et al. (2011) reported 11 triterpene acids [4 oleanane type: oleanolic acid, maslinic acid, 3-epiasiatic acid and δ-oleanolic acid; 5 ursane-type: ursolic acid, methyl ursolate, corosolic acid, 3-O-(E)-pcoumaroyl tormentic acid and euscaphic acid; 2 lupane-type: betulinic acid and methyl betulinate] from the methanolic leaf extract. Wu et al. (2013) identified total 12 compounds such as euscaphic acid, 2α, 19α-dihydroxyurs-3-oxo-urs-12-en-28-oic acid, 3-O-p-coumaroyltormentic acid, maslinic acid, 2α-hydroxyursolic acid, linolenic acid, hyptadienic acid, linoleic acid, 3β-O-coumaroyl-2α-hydroxy-urs-12-en-28-oic acid, oleanolic acid, ursolic acid and palmitic acid from the leaves using UPLC-QTOF/MS. Rashed and Butnariu (2014) identified 3 triterpenic acids (oleanolic, ursolic, and corosolic acids) and 4 flavonoids (naringenin, quercetin, kaempferol 3-O-β-glucoside and

quercetin 3-O-α-rhamnoside) from the methanolic stem extract. Tan et al. (2017a) identified new triterpene (3β-hydroxyl-21β-acetoxyl-urs-12-en-28-carboxylate) along with known 7 triterpenoids (methyl corosolate, ursolic acid, oleanolic acid, methyl maslinate, α-amyin, 3β,19α,23-trihydroxy-urs-12-ene and uvaol) from the leaves. Zhang et al. (2019) reported eight compounds *viz.* euscaphic acid, 2α,19α-dihydroxy-3-oxo-urs-12-en-28-oic acid, 3-O-trans-p-coumaroyltormentic acid, 3-O-cis-p-coumaroyltormentic acid, maslinic acid, corosolic acid, oleanolic acid and ursolic acid from triterpenoid composition of leaves extract. Wei et al. (2019) identified 13 triterpenoid acids *viz.* 3β-O-cis-p-coumaroyl-2α-hydroxy-12-ursen-28-oic acid, jacoumaric acid; 3-O-trans-feruloyl euscaphic acid, 2α,3α,19α,23-tetrahydroxy-12-ursen-28-oic acid, euscaphic acid, ursolic acid, maslinic acid, corosolic acid, arjunic acid, 2α,3α-dihydroxy-12-ursen-28-oic acid, oleanic acid, 2α,3α,23-trihydroxyolean-12-en-28-oic acid and 3-O-cis-p-coumaroyltormentic acid from leaves.

Phenolic compounds like ferulic acid, neochlorogenic acid, protocatechuic acid, chlorogenic acid, 4-hydroxybenzoic acid, 4-O-caffeoylquinic acid, caffeic acid, ellagic acid and o-coumaric acid reported from the fruits using HPLC (Xu et al., 2014). Zhang et al. (2015) quantified 11 phenolic compounds (3-p-coumaroylquininc acid, 5-caffeoylquinic acid, 4-caffeoylquinic acid, 3-caffeoylquinic acid, 5-feruloylquinic acid, quercetin-3-O-galactoside, quercetin-3-O-glucoside, quercetin-3-O-rhamnoside, kaempferol-3-O-galactoside, kaempferol-3-O-rhamnoside and kaempferol-3-O-glucoside) from peel and pulp of different cultivars from China. Park et al. (2019) also identified 4 new polyphenol compounds (5-O-caffeoylshikimic acid, 4-O-caffeoylshikimic acid, naringenin-6-C-(2″-O-acetyl)-glucoside and naringenin-6-C-(2″,4″,6″-O-triacetyl)-glucoside) along with chlorogenic acid, epicatechin, quercetin-3-O-galactoside and quercetin-3-O-glucoside from the leaves. Li et al. (2016) summarized previously reported phenolic compounds from the fruit. Flavonols [quercetin, quercetin 3-O-rhamnoside (quercitrin), quercetin-3-O-glucoside (Isoquercitrin), quercetin-3-O-rutinoside (rutin), quercetin-3-O-galactoside (hyperoside), quercetin-3-O-neohesperidoside, quercetin-3-O-sophoroside, quercetin-3-O-sambubioside, quercetin-3-O-galactosyl-(1→6)-glucoside, kaempferol-3-O-glucoside, kaempferol-3-O-rutinoside, kaempferol-3-O-neohesperidoside, kaempferol-3-O-sambubioside, kaempferol-3-O-rhamnoside, kaempferol-3-O-sophoroside, kaempferol-3-O-α-rhamnopyranosyl-(1→2)-β-d-glucopyranoside, kaempherol-3-O-α-l-(2″,4″-di-E-feruloyl)-rhamnoside, kaempherol-3-O-α-l-(2″,4″-di-E-pcoumaroyl)-rhamnoside and kaempherol-3-O-α-l-(2″,4″-di-

Z-pcoumaroyl)-rhamnoside]; flavan-3-ol [epicatechin and epigallocatechin gallate]; phenolic acids [2-hydroxybenzoic acid, p-hydroxybenzoic acid, protocatechuic acid, gallic acid, caffeic acid, chlorogenic acid, cryptochlorogenic acid, neochlorogenic acid, o-coumaric acid, p-coumaric acid, 3-p-coumaroyl quinic acid, 4-p-coumaroyl quinic acid, 5-p-coumaroyl quinic acid, ferulic acid, 4-feruloylquinic acid, 5-feruloylquinic acid, (6R,9R)-3-oxo-α-ionyl-9-O-β-dglucopyranosyl, eriojaposide A, eriojaposide B, (6S,9R)-roseoside OH β-d-Glucopyranosyl, (6S,9R)-vomifoliol-9-O-β-dapiofuranosyl-(1″→6′)-β-dglucopyranosyl and (6S,9R)-vomifoliol-9-O-β-dxylopyranosyl-(1″→6′)-β-dglucopyranosyl]. Recently, Zhang et al. (2021) determined phytochemicals from different plant parts using UHPLC-QTOF-MS. They identified total 349 compounds which belong to phenolic acids, flavonoids, stilbenes, lignans, and terpenoids.

Number of carotenoids such as neoxanthin, violaxanthin, luteoxanthin, 9-cis-violaxanthin, lutein, phytoene, phytofluene, β-cryptoxanthin, β-carotene and ζ-carotene have been reported from fruit using HPLC-PDA (Zhou et al., 2007; Fu et al., 2012). Koshioka et al. (1988) identified gibberellins (A_9, A_{15}, A_{19}, A_{20}, A_{29}, A_{35}, A_{44}, A_{50}, and A_{61}) from immature seeds using GC/SIM. Along with gibberellic acid, other compounds like methyl ester trimethylsilyl ether derivatives, C-11β hydroxylated GA_9 and dehydro-GA_{35} were also detected. Further, Yuda et al. (1992) identified gibberellic acids (GA_9, GA_{15}, GA_{24}, GA_{35}, and GA_{50}) and 6 GA-like substances (GA_{80} (11β-hydroxy-GA_7); GA_{84} (11β-hydroxy-GA_9); dehydro-GA_{25}; dehydro-GA_{24}; GA_{24}-like and GA_{23}-like) from the immature seed and pericarp.

Essential oil of fresh flowers recorded 30 compounds such as nonane, hexadecane, heptadecane, octadecane, nonadecane, eicosane, heneicosane, docosane, tricosene, tricosane, tetracosane, pentacosene, pentacosane, hexacosane, heptacosane, octacosane, nonacosane, hexadecanal, octadecanal, 6.10.14-trimethyl-2-pentadecanone, 4-methoxy methylbenzoate, 4-methoxy ethylbenzoate, phenyl ethyl octanoate, nerolidol, tetradecanoic acid, methyl hexadecanoate, hexadecanoic acid, methyl linoleate, p-anisaldehyde, and butylated hydroxytoluene (Merle and Boira, 2003). Sun et al. (2020) reported 83 volatile compounds *viz.*, pentanal; hexanal; 2-hexenal,(E)-; 2-heptenal,(E)-; octenal,(E)-; 2-decenal,(Z)-; decanal; nonanal; octanal; citral; 2-nonenal,(E)-; citronellal; β-cyclocitral; furfural; 3-hexenal,(Z); heptanal; 2,6-nonadienal,(E,Z)-; benzaldehyde; 2,4-nonadienal,(E,E)-; dodecanal; ethanol; 1-pentanol; eucalyptol; 1-hexanol; 2-hexen-1-ol, (E)-; 3-hexen-1-ol, (Z)-; 2-furanmethanol; octanol; 1-nonanol; 1-octen-3-ol; citronellol; linalool; terpinen-4-ol; 1-heptanol; 2-ethylhexanol; 2-hepten-1-ol,(E)-; 2-hexanol;

2-octen-1-ol, (E)-; a-terpineol; nerol; α-pinene; α-thujene; camphene; γ-terpinene; cis-β-ocimene; β-pinene; sabinene; β-myrcene; α-terpinene; D-limonene; β-phellandrene; P-cymene; terpinolene; 2-heptanone, 4-methyl-; 3-octanone; 1-octen-3-one; 5-hepten-2-one, 6-methyl-; geranyl acetone; β-ionone; 2(3H)-furanone, 5-methyl-; acetic acid; 2-methylbutanoic acid; methyl butanoate; methyl 2-methylbutanoate; butyl acetate; methyl hexanoate; methyl octanoate; hexyl hexanoate; ethyl 2-methyloctanoate; methyl benzoate; ethyl benzoate; ethyl hexanoate; ethyl octanoate; octyl acetate; benzene, 1,2,3,5-tetramethyl-; benzene, (1-methylethyl)-; benzene, 1,2,3-trimethyl-; benzene, 1,2,4,5-tetramethyl-; styrene; furan, 2-pentyl-; naphthalene; ethyl carbitol and oxime, methoxy-phenyl-from white and red fleshed fruits using HS-SPME and combined analysis of electronic nose and GC-MS (Figures 26.1–26.5).

26.3 PHARMACOLOGY

26.3.1 ANTIOXIDANT ACTIVITY

Lee and Kim (2009) noted strong scavenging (SC_{50} 1.71 and 2.11 mg/mL) and nitric oxide (NO) scavenging (83.9 and 82.2%) activities from raw and freeze-dried leaf ethanolic extracts, respectively. Zhou et al. (2011a) analyzed the antioxidant potential of methanolic, ethanolic, acetone, n-butyl alcohol and ethyl alcohol extracts of flower. Methanolic extract exhibited FRAP, DPPH, and ABTS radical scavenging activities, i.e., 4.46 ± 0.08, 7.07 ± 0.01, and 11.67 ± 0.09 VCEAC mg/g DW followed by ethanolic (2.32 ± 0.28, 3.31 ± 0.20, and 4.06 ± 0.14 VCEAC mg/g DW), acetone (0.80 ± 0.03, 1.15 ± 0.14, and 1.84 ± 0.18 VCEAC mg/g DW) n-butyl alcohol (0.65 ± 0.05, 0.91 ± 0.04, and 1.45 ± 0.14 VCEAC mg/g DW) and ethyl alcohol (0.42 ± 0.10, 0.55 ± 0.07, and 1.01 ± 0.20 VCEAC mg/g DW) extract, respectively. Among four different stages of flower, stage 3 showed the highest antioxidant potential, i.e., 3.61 ± 0.21, 5.19 ± 0.41, and 6.48 ± 0.08 VCEAC mg/g DW for FRAP, DPPH, and ABTS. They also recorded the highest antioxidant capacity in terms of FRAP, DPPH, and ABTS from the petals (4.24 ± 0.04, 6.73 ± 0.04, and 7.19 ± 0.17 VCEAC mg/g DW of the peduncle, pistil + stamen and sepal. Zhou et al. (2011b) analyzed fruits of 24 cultivars for their antioxidant potential wherein Dahongpao II showed highest hydrophilic and lipophilic antioxidant activity (121.64 and 6.87 TEAC mg/100 g FW, respectively). Xu and Chen (2011) recorded antioxidant capacity of 12 cultivars from

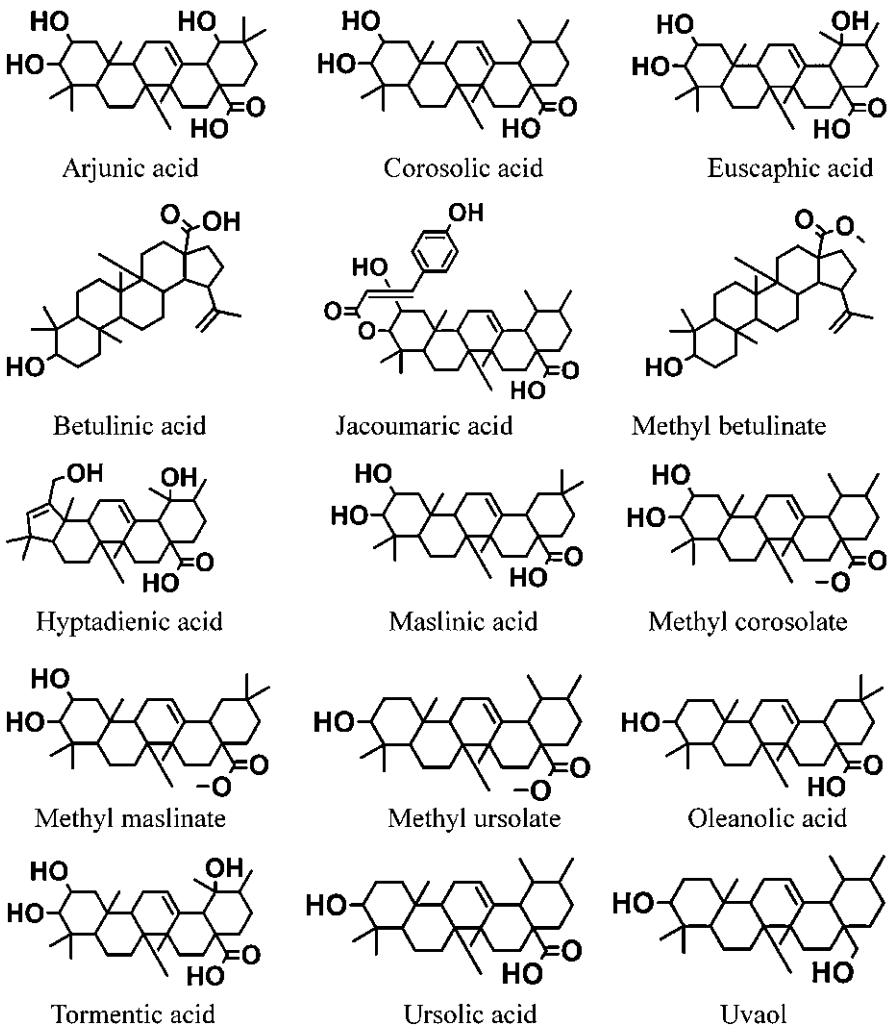


FIGURE 26.1 Terpenes from *Eriobotrya japonica.*

China, among them highest antioxidant potential recorded in Bingtangzhong cultivar with 4.24 ± 0.14 and 2.71 ± 0.23 μmol TE/g of DPPH and ABTS, respectively. Similarly, Tianzhong cultivar recorded highest FRAP reducing potential (3.72 ± 0.19 μmol TE/g).

Six different cultivars fruits (Ninghaibai, Taipingbai, Daguotaipingbai, Taxiabai, Taxiahuang, and Taxiahong) from China were studied for their antioxidant capacities (Xu et al., 2014). Authors recorded 2.91 ± 0.32 to

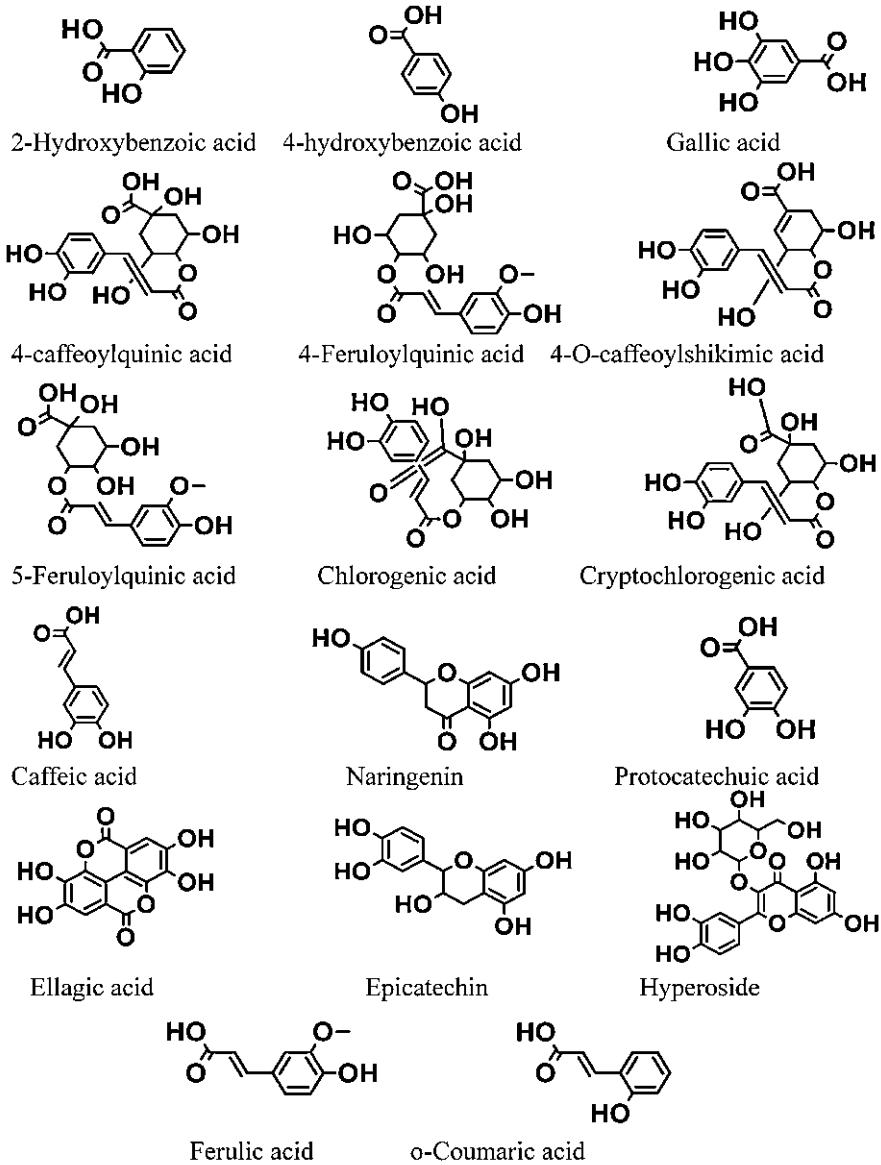


FIGURE 26.2 Phenols and flavonoids from *Eriobotrya japonica.*

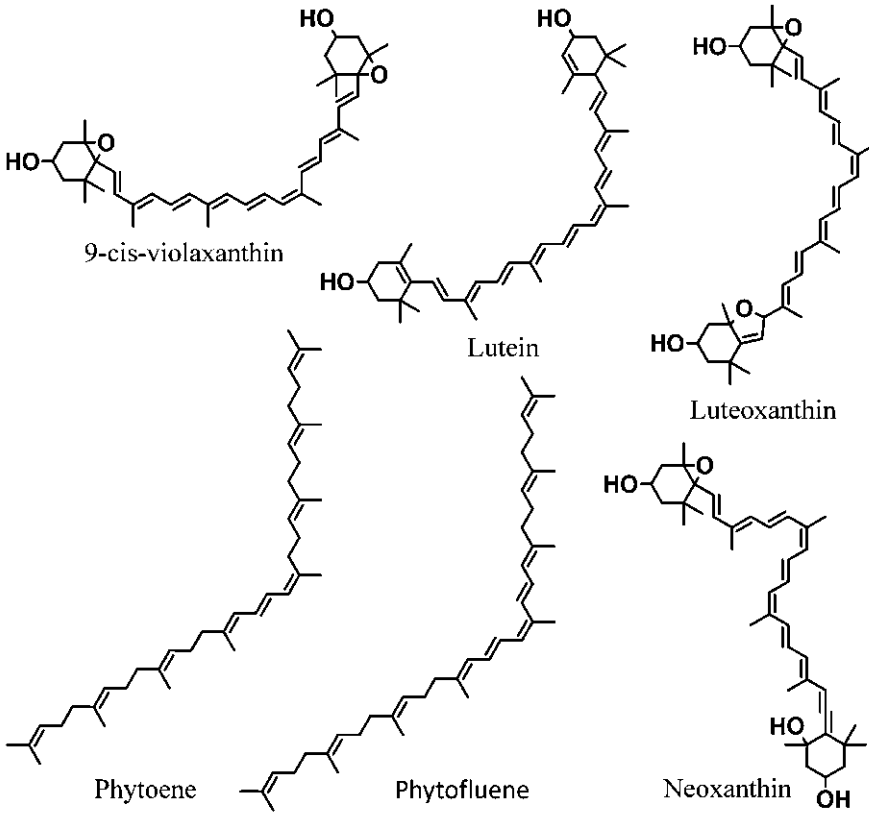


FIGURE 26.3 Carotenoids from *Eriobotrya japonica.*

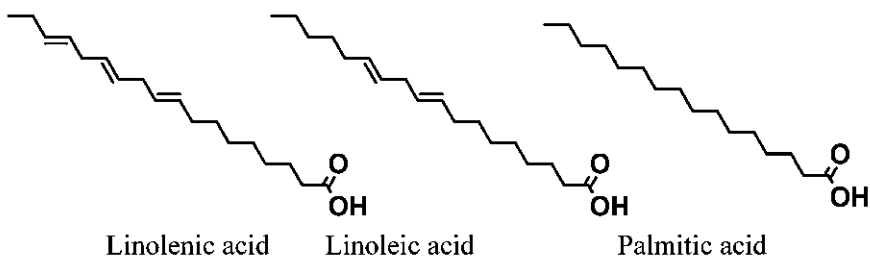


FIGURE 26.4 Fatty acids from *Eriobotrya japonica.*

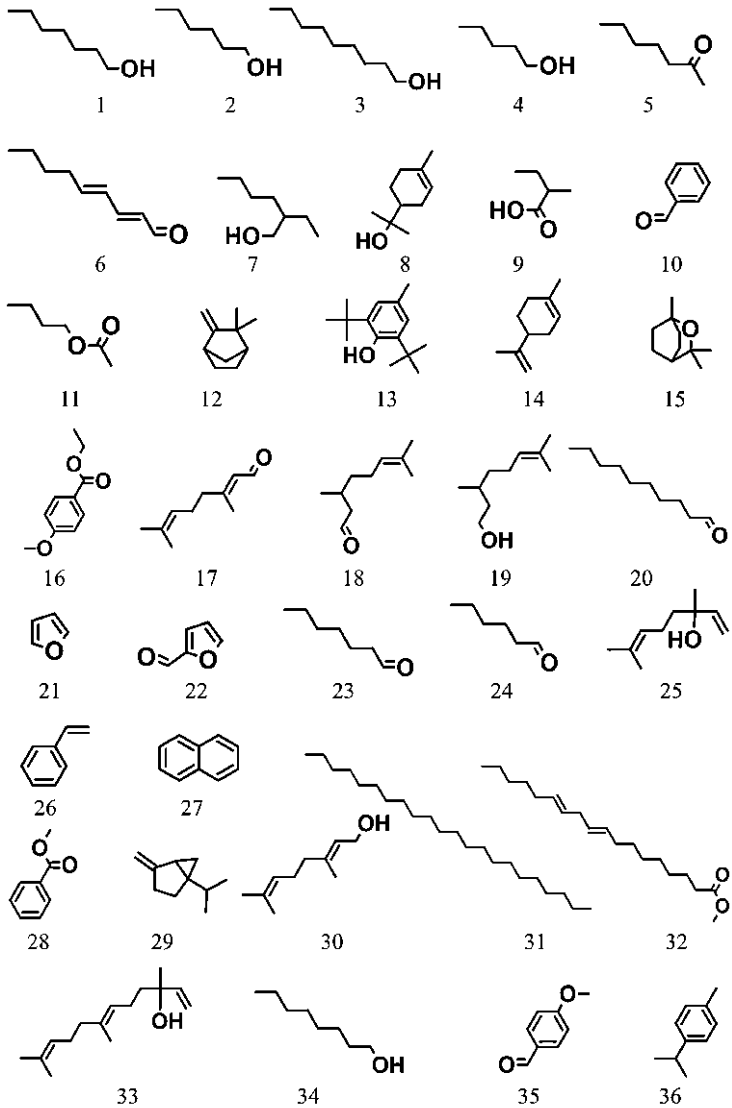


FIGURE 26.5 Volatiles from *Eriobotrya japonica*. (1) 1-Heptanol; (2) 1-hexanol; (3) 1-nonanol; (4) 1-pentanol; (5) 2-heptanone; (6) 2,4-nonadienal; (7) 2-ethylhexanol; (8) α-terpineol; (9) 2-methylbutanoic acid; (10) benzaldehyde; (11) butyl acetate; (12) camphene; (13) butylated hydroxytoluene; (14) D-limonene; (15) eucalyptol; (16) 4-methoxy ethylbenzoate; (17) citral; (18) citronellal; (19) citronellol; (20) decanal; (21) furan; (22) furfural; (23) heptanal; (24) hexanal; (25) linalool; (26) styrene; (27) naphthalene; (28) methyl linoleate; (29) sabinene; (30) nerol; (31) docosane; (32) methyl linoleate; (33) nerolidol; (34) octanol; (35) p-anisaldehyde; and (36) P-cymene.

4.93 ± 0.26 μmol TE/g FW of DPPH radical scavenging ability and 3.16 ± 0.34 to 5.09 ± 0.31 μmol TE/g FW of ferric reducing power in Ninghaibai. Similarly, ABTS radical scavenging was highest (2.73 ± 0.22 to 4.55 ± 0.20 μmol TE/g FW) in Taxiahong. Zhang et al. (2015) analyzed antioxidant potentials from 7 different cultivars peel and pulp using DPPH, ABTS, and FRAP assay. Antioxidant potency composite index confirmed the cultivars from Dahongpao (APC index, 100 for peel) and Luoyangqing (APC index, 97.95 for pulp) locality. Antioxidant potential from the extracts obtained from different plant parts were studied by several researchers (Kaur et al., 2015; Mokdad-Bzeouich, 2015; Lee et al., 2016; Turola et al., 2018; Seong et al., 2019; Zhang et al., 2021).

26.3.2 ANTI-DIABETIC ACTIVITY

Shih et al. (2010) fed a high-fat diet (45%) to mice for 10 weeks. After 4 weeks, oral administration of leaves extract (1.0 g/kg/day) with high-fat diet revealed significant decrease in the body weight, reduced food intake, reduction in body weight gain, decreased the liver weights, increased plasma glucose level, reduced plasma free fatty acid and triglyceride, increased leptin and insulin indicating induced hyperglycemia, hyperleptinemia, hyperinsulinemia, and hypertriglyceridemia. Flower extracts (0.5 and 1.0 g/kg) were also evaluated for antidiabetic activity using streptozotocin (STZ)-induced diabetic mice. The significant reduction in glucose level after 30, 60, 90, and 120 min of glucose loading. They noted significant reduction of blood glucose, HbA1C, total cholesterol and plasma triglyceride, whereas increase in insulin level (Lin et al., 2018).

26.3.3 ANTIBACTERIAL ACTIVITY

Ethanolic raw leaf extract (80%) showed promising antimicrobial activity against *Staphylococcus aureus, S. epidermidis, Bacillus cereus, B. subtilis, Vibrio vulnificus* and Methicillin-resistant *S. aureus* with 18.5 ± 0.5, 14.0 ± 1.0, 13.0 ± 0.5, 12.0 ± 0.5, 10.5 ± 0.5, and 24.0 ± 0.0 mg/g, respectively (Lee and Kim, 2009). Antimicrobial activity from methanolic extract against different bacterial and fungal strains were also evaluated by Rashed and Butnariu (2014). Among them, *Candida albicans* showed significant growth inhibition (less than 20 μg/mL of MIC). Tan et al. (2017b) evaluated 18 triterpenoids from methanol extract of leaves (100 μg/mL) against

Propionibacterium acnes. Ursolic acid, oleanolic acid, methyl corosolate, maslinic acid, corosolic acid, pomolic acid, tormentic acid, euscaphic acid, 6,19-dihydroxyurs-12-en-3-oxo-28-oic acid, hyptadienic acid, 3-O-trans-p-coumaroyltormentic acid and 3-O-cis-p-coumaroyltormentic acid found effective with 109.8 ± 0.5, 100.4 ± 0.8, 77.9 ± 1.6, 104.1 ± 3.1, 105.9 ± 0.4, 84.4 ± 1.2, 102.8 ± 2.1, 98.5 ± 1.3, 87.6 ± 7.4, 103.9 ± 3.1, 101.4 ± 2.1, and 103.5 ± 2.2% inhibition rate. Rao and Tang (2017) synthesized silver nanoparticles from aqueous leaves extract (100 mg/L) and found 2.5 and 4.5 mm zone of inhibition against *Escherichia coli* and *Staphylococcus aureus*, respectively.

26.3.4 NEUTROPHIL ELASTASE ACTIVITY

Zhang et al. (2019) evaluated leaves extract (triterpenoid composition and ursolic acid) for *in vitro* human neutrophil elastase inhibitory activity on acute lung injury using lipopolysaccharide (LPS)-induced lung inflammatory model in mice. They recorded significant activity for both triterpenoid composition and ursolic acid with IC_{50} values of 3.26 ± 0.56 and 8.49 ± 0.42 μg/mL, respectively compared with positive control ONO-5046 ($IC_{50,}$ 266.87 ± 45.10 nM).

26.3.5 ANTITUSSIVE ACTIVITY

Fallen and growing leaves aqueous and ethanol extracts were examined for antitussive activity using a classical mouse cough model induced by ammonium hydroxide. Oral administration of extract (2.5 and 5 g of crude drug/kg body weight/day) to 6-week-old male ICR mice used to investigate antitussive effects. They recorded the best activity from 5 g of crude drug/kg of mouse body weight/day of fallen leaves of ethanolic extract for delayed cough incubation period and decrease the cough frequency (Wu et al., 2018).

26.3.6 EXPECTORANT ACTIVITY

Wu et al. (2018) evaluated the expectorant activity of fallen and growing leaves aqueous and ethanol extracts. Orally administrated with 2.5 and 5 g of crude drug/kg body weight/day for 3 days to Six-week-old male ICR mice. Among the different extracts, aqueous extracts (5 g of crude drug/kg of mouse body weight/day) of growing leaves exhibited effective expectorant activity.

26.3.7 BUTYRYL CHOLINESTERASE INHIBITORY ACTIVITY

Among the root, leaf, stem, seed, and fruit, roots showed strong butyryl cholinesterase inhibitory activity (3.64 mg galantamine equivalent/g) (Zhang et al., 2021).

26.3.8 ANTI-MELANOGENESIS ACTIVITY

Tan et al. (2017b) evaluated anti-melanogenesis activity (inhibitory effects on melanin synthesis and cell viability) on B16 mouse melanoma cell line using 18 triterpenoids isolated from methanolic leaf extract. They noted eight compounds *viz*. ursolic acid, oleanolic acid, betulinic acid, methyl maslinate, methyl corosolate, maslinic acid, corosolic acid and tormentic acid revealed appreciable melanin synthesis inhibitory activity (IC_{50} 4.8, 26.8, 11.8, 12.8, 16.1, 18.5, 18.7, and 18.5 µM, respectively) with low cytotoxicity (S.I.>1.0). Seong et al. (2019) performed melanogenesis inhibition test of leaf ethanol extract on B16F1 mouse melanoma cells induced with α-MSH (100 nM). They noted significant inhibition of melanin content at 0.05 and 0.1% (w/v) plant extract (52.9 ± 6.9 and 29.7 ± 2.8%, respectively).

26.3.9 ANTI-ALLERGIC ACTIVITY

Tan et al. (2017b) analyzed the anti-allergic activity of 18 triterpenoids isolated from methanol extract of leaves. The activity was studied by measuring the release of β-hexosaminidase from IgE-stimulated RBL-2H3 mast cells. Ursolic acid, 3-epicorosolic acid, euscaphic acid and maslinic acid significantly suppressed the release of β-hexosaminidase (72.5, 54.4, 74.5, and 66%, respectively) with IC_{50} value of 39.5, 14.2, 15.8, and 22.8 µM, respectively.

26.3.10 ANTI-AGING ACTIVITY

Triterpenoids from leaves were used to study the activity by measuring collagen and hyaluronic acid production (Tan et al., 2017b). Methyl corosolate and corosolic acid induced type I collagen production (3.4- and 3.6-fold) at 10 µg/mL. Similarly, corosolic acid and pomolic acid showed strongest hyaluronic acid stimulating activity (5.9- and 5.8-fold) at 10 µg/mL concentration followed by methyl corosolate (3.5-fold at 10 µg/mL) and ursolic acid (4.7 fold at 5 µg/mL).

26.3.11 ANTICANCER ACTIVITY

Taniguchi et al. (2002) evaluated the cytotoxicity of callus triterpenes against human oral tumor cell lines (HSC-2 and HSG). Ursolic acid, 3-O-cis-pcoumaroyltormentic acid, maslinic acid, tormentic acid, mixture of 3-O-trans-p-coumaroyltormentic acid and hyptadienic acid 2α-hydroxyursolic acid, noted significant cytotoxic activity against HSC-2 (CC_{50} 29, 22, 21, 21 18, and 10 µg/mL, respectively) and HSG (CC_{50} 48, 30, 26, 25, and 18 and 12 µg/mL, respectively). Further, they also evaluated the effect of triterpenes on the activation of Epstein–Barr virus early antigen induced by TPA (20 ng/mL). Ursolic acid, hyptadienic acid, oleanolic acid, 19α-dihydroxy-3-oxo-urs-12-en-28-oic acid, maslinic acid and mixture of 3-O-cis-pcoumaroyltormentic acid and 3-O-trans-p-coumaroyltormentic acid showed more than 65% inhibition at 500 mol ratio/TPA. In addition, authors also performed a two-stage carcinogenesis test on 6 weeks old ICR female mouse skin. 19α-dihydroxy-3-oxo-urs-12-en-28-oic acid showed a 40% decrease in an average number of papillomas, indicating antitumor activity. Ito et al. (2002) identified active compounds (Roseoside and procyanidin B-2) from leaves and assessed for *in vivo* two-stage carcinogenesis assay on mouse skin. They recorded significant inhibition of TPA induced tumor promotion for mice bearing papillomas and number of papillomas per mouse. Four triterpenes (ursolic acid, corosolic acid, oleanolic acid and maslinic acid) from leaves were evaluated for anti-proliferative activity in human leukemia (HL) cell lines. Corosolic acid and ursolic acid significantly suppressed cell growth in all leukemia cell lines. Corosolic acid-induced anti-proliferative effect against leukemia cells showed chromatin condensation, DNA fragmentation and increased in the sub-G1 phase (16.4 and 61.6% for 12 and 24 hours, respectively). These findings revealed the anti-proliferative effect of corosolic acid through induction of apoptotic cell death (Uto et al., 2013).

You et al. (2016) investigated the effect of ethanolic and water extracts of leaves (500 mg/kg) on female athymic nude mice with MDA-MB-231 cells. They noted significant reduction in tumor growth, cell division, inhibition of MDA-MB-231 cell proliferation and increased apoptosis. In addition, inhibitory effect on adhesion, migration, and invasion were also noted. Lee et al. (2016) evaluated anti-proliferation activity of the seed, fleshy seedless fruit and leaf ethanolic extract on liver cancer (H460), stomach cancer (AGS) and lung cancer cell line (A549). They noted significant antiproliferation effect for all selected cell lines. Li et al. (2017a) evaluated acute (0.30, 0.65, 1.39, and 3.00 g/kg body weight) and subacute (150, 300, and 600 mg/kg BW)

toxicity of triterpene acid of leaves on ICR male and female mice and found no mortality and toxicity. Recently, Jabir et al. (2021) synthesized silver nanoparticles from leaves and tested against human cancer lines (MCF-7 and HeLa). They noted a significant decrease in the proliferation of cancer cells after 72 hours (75 and 65%) with IC_{50} values of 18.05 and 21.69, respectively, and confirmed the induction of apoptosis through p53 pathway.

26.3.12 ANTI-INFLAMMATORY ACTIVITY

Cha et al. (2011) performed anti-inflammatory property of n-BuOH leaves fraction (500 g/mL) using IFN-γ/LPS activated murine peritoneal macrophage model and noted suppressed NO production (87.7%) and iNOS expression through via down-regulation of NF-$_k$B activation. Tan et al. (2017b) isolated 8 triterpenoids from the leaves and accessed for PDE4D inhibitory assay. Amongst them, ursolic acid, methyl corosolate and uvaol significantly inhibited PDE4D (IC_{50} 2.18, 3.06, and 5.17 μM, respectively). These findings proposed a novel mechanism for the anti-inflammatory activity. Seong et al. (2019) estimated the anti-inflammatory activity of the leaf ethanolic extract by NO assay and TNF-α measurement using RAW 264.7 macrophage cells with induced LPS (1 μg/mL). They recorded 69.24 ± 2.75, 39.54 ± 1.70, and 35.25 ± 1.81% inhibition at 0.125, 0.25, and 0.5% (w/v) plant extract, respectively. Similarly, 889.74 ± 11.96, 888.39 ± 7.16, and 839.43 ± 6.81 pg/mL of TNF-α release by plant extract was observed at 0.125, 0.25, and 0.5% (w/v) concentration, respectively. Recently, Jabir et al. (2021) reported that silver nanoparticles synthesized from leaves significantly decreased the level of IL-1b and IL-6. Tormentic acid from suspension cells was evaluated on male ICR mice for anti-inflammatory potentials. Tormentic acid (2.5 mg/kg) significantly decreased paw edema induced by carrageenan on 4th and 5th hour. They also found that tormentic acid significantly inhibited RAW264.7 cell viability (5 μg/mL), LPS-induced nitrate production (2.5 μg/mL), inhibited NO synthase and cyclooxygenase-2 (2.5 μg/mL, 53.2 and 47.6%, respectively) protein expression and decreased thiobarbituric acid reactive substances (TBARS) level (2.5 mg/kg) (Chang et al., 2011).

26.3.13 ANTIOSTEOPOROSIS ACTIVITY

Oral administration of 5% leaves extract along with the normal diet to ovariectomized mice for evaluation of body weight and bone mineral density.

Significant inhibition was recorded in bone mineral density in the trabecular cells of the head, abdomen, and lumbar parts but did not find any difference in body weight (Tan et al., 2014). They also investigated osteoclast differentiation using different concentrations of leaves methanolic or water extracts (50, 125, 250, and 500 μg/mL) to RAW 264.7 cells. Authors recorded significant inhibition of multinucleated osteoclast-like cells by the methanolic extract without any cytotoxicity. Through fractionation, confirmed inhibition of osteoclast differentiation by ursolic acid. Potent triterpenoids from the leaves were subjected to investigate the antiosteoclastogenesis activity (Tan et al., 2015). Ursolic acid, methyl maslinate, methyl corosolate, pomolic acid, aslinic acid, corosolic acid, tormentic acid, euscaphic acid, 3-oxours-12-en-28-oicacid, mixture of 3-O-trans(cis)-p-coumaroyl tormentic acid methyl ester showed osteoclast differentiation on RAW.264.7 cells (IC_{50} 5.4, 15.9, 25, 10.6, 12.9, 10.6, 22.8, 35.5, 33, 27.9, and 29.2 μM, respectively) when compared with oleic acid as a positive control (IC_{50} 40.1 μM).

26.3.14 SKIN AND EYE IRRITATION TEST

Skin irritation test using ethanolic leaves extract by reconstructed human epidermis model noted nonirritant with 98.9 ± 2.0% cell viability. The eye irritation using bovine corneal opacity and permeability assay confirmed the no opacity and permeability increase grossly with 2.2 ± 0.5 irritancy score. Similarly, eye irritation by hen's egg testchorioallantoic membrane assay revealed no hemorrhage, coagulation, and lysis. The results directed the use of *E. japonica* ethanolic leaf extract as a cosmetic ingredient in skin improvement (Seong et al., 2019).

26.3.15 MALE CONTRACEPTIVE ACTIVITY

Effect of the oral administration of aqueous leaf extract on the fertility of male Balb/c mice was investigated by Al Moubarak et al. (2020). Animals treated with plant extract for 10 and 30 days showed significant decrease in sperm motility (44.5 and 68.4%), viability (28.4 and 67.2%) and sperm count (66 and 86.7%), reduction in level of testosterone (48.8 and 87.3%), progesterone (88.3% for 30 days) and increased in prolactin level (66.8 and 67%), respectively. Significant restoration of sperm motility (65%), viability (63%), sperm count (85%), testosterone (79%), progesterone (82%) and prolactin (47%) were observed after 20 days of treatment. Histopathological

investigation confirmed the decrease in a number of spermatozoa, diameter of seminiferous tubules and destruction of germinal epithelium after 10 and 30 days of administration of plant extract and restored after 20 days.

26.3.16 HEPATOPROTECTIVE ACTIVITY

The hepatoprotective property of isolated tormentic acid on acetaminophen-induced liver damage in mice was studied (Jiang et al., 2017). Tormentic acid administrated 6 days before acetaminophen-induction (1.25, 2.5, and 5 mg/kg) noted significant prevention of the elevation of total cholesterol, total bilirubin, triacylglycerol, alanine aminotransferase and serum aspartate aminotransferase. Histopathology of the liver confirmed the decreases in necrotic areas and hepatocellular degeneration. They also recorded significantly preventing increase in the TBARS levels, reduction in ROS and NO production, supressed the Serum IL-1b, IL-6 and TNF-a levels. Results confirmed the preventing the acetaminophen-induced liver injury by tormentic acid. Li et al. (2017b) purified and isolated tormentic acid from suspension cell culture and evaluated against hepatocellular carcinoma cells (HepG2, Bel-7405, Sk-hep-1). Tormentic acid (15 μg/mL) showed significant antiproliferative activity whereas tormentic acid (22.5 μg/mL) showed a decrease in colony forming ability towards HepG2 and Sk-hep-1 cells. Bel-7405 and Sk-hep-1 cells migrated about 2/3 and 1/2 of the cell-free scratch lines. Tormentic acid (15 μg/mL) showed significant decreases in the average number of transmembrane cells (HepG2, Sk-hep-1 and Bel-7405). They also confirmed significant increased induction of apoptosis which confirmed the anti-cancer activity of tormentic acid.

26.3.17 ANTI-ALLERGIC ACTIVITY

Kim et al. (2009) evaluated the effect of leaves extract (0–1,000 mg/kg) on the anaphylactic allergic reaction in mice. They recorded decreased IgE-mediated passive cutaneous anaphylaxis and histamine release in mast cells. They also noted decreased production of tumor necrosis factor-α in human mast cells, indicating *E. japonica* as an anti-allergic agent. Recently, Jabir et al. (2021) synthesized silver nanoparticles from leaves and male mice were treated to test anti-allergic potential. They noted significantly decreased eosinophil numbers, IgE, and IFN-γ levels

as compared to ovalbumin (OVA) challenged group, suggested decreased allergic disorder.

26.3.18 ANTIGENOTOXIC ACTIVITY

Mokdad-Bzeouich (2015) evaluated the antigenotoxic potential of aqueous leaves extracts (50, 250, and 500 mg/plate) in genotoxicity induced with nitrofurantoin and aflatoxin B1. The extract (500 mg/plate) exhibited significant genotoxicity with IC_{50} values of 140 and 240 mg/assay.

26.3.19 ANTIMUTAGENIC ACTIVITY

Mokdad-Bzeouich (2015) evaluated antimutagenic potential against *S. typhimurium* TA104 from aqueous leaves extracts (50, 250, and 500 mg/plate). They noted highest protective effect against methyl methane sulfonate and 2-aminoanthracene with IC_{50} values of 80 and 140 mg/plate.

26.3.20 CARDIO-PROTECTIVE ACTIVITY

Effect of leaf extract (100 and 300 mg/kg BW, two doses per week) against hypertension-induced cardiac apoptosis and fibrosis in 12-week-old spontaneously hypertensive male rats was studied for 8 weeks (Chiang et al., 2018). According to echocardiographic assessment, ejection fraction and fraction shortening level were significantly rescued when supplemented with both the doses. The TUNEL assay confirmed the reduction in TUNEL positive cells, attenuated cardiac apoptosis and fibrosis when supplemented with plant extract, indicating cardio-protective property.

26.3.21 ANTINOCICEPTIVE ACTIVITY

Cha et al. (2011) examined the antinociceptive property of n-BuOH leaves fraction using different experimental models. The tail immersion test confirmed the most prominent analgesic activity (23.06%) after 90 min of 250 mg/kg of extract administration. Hot plate test showed an increase in analgesia 71.62 and 77.92% at 60 min using 250 and 500 mg/kg of extract, respectively. In acetic acid test, 71.50% reduction in a number of writhing

was observed at 500 mg/kg dose. Similarly, the formalin test showed 42.87 and 74.84% mean licking time in the first phase and second phase, respectively, at 500 mg/kg dose. These results supported the antinociceptive potential of the plant.

26.3.22 NEUROPROTECTIVE ACTIVITY

Bae et al. (2014) examined the combined effect of *E. japonica* leaves and *Salvia miltiorrhiza* roots on neuroprotective affect. Mixture of leaf ethanol and root water extracts (30 μg/mL) offered protection from Aβ-induced toxicity (81.31 ± 5.73%) and $CoCl_2$-induced hypoxia in SH-SY5Y cells (81.31 ± 5.73%). Corticosterone-induced impairment on SH-SY5Y cells noted 76.32 ± 6.54% cell viability. Mixture of leaves ethanol and root water extracts (30 μg/mL) suppressed $A\beta_{1–42}$-induced caspase-3 activity of SH-SY5Y cells (81.31 ± 6.54%). $A\beta_{1–42}$-induced impairments of memory acquisition and retention in the Morris water maze test significantly decreased escape latencies for a mixture of 100 mg/kg. At the same concentration, $A\beta_{1–42}$-induced behavioral deficits showed significant memory impairment (129.35 ± 21.55 sec), indicating neuroprotective against $A\beta_{1–42}$-induced neuronal toxicity.

26.3.23 APOPTOTIC CELL DEATH ACTIVITY

Kikuchi et al. (2011) evaluated 11 triterpene acids from leaves methanolic extract on DNA topoisomerase inhibitory activity, cytotoxicity against human leukemia (HL60) and melanoma cell lines (CRL1579). Compounds like δ-oleanolic acid, ursolic acid, 3-O-(E)-pcoumaroyl tormentic acid and betulinic acid revealed significant topoisomerase inhibitory activity (IC_{50} 20.3–36.5 mM) and cytotoxicity against HL60 cell line (EC_{50} 5.0–8.1 mM). 3-O-(E)-pcoumaroyl tormentic acid (40 mM) also induced early and late apoptosis by DNA fragmentation after 48 hours (25.7 and 19.2%, respectively). Western blot analysis also confirmed the apoptotic cell death through activation of caspases-3 and 9 in HL60 cell line.

KEYWORDS

- **bioactives**
- **cytotoxicity**
- **DNA topoisomerase inhibitory activity**
- ***Eriobotrya japonica***
- **essential oil**
- **human leukemia**
- ***Photinia japonica***

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CHAPTER 27

Fagopyrum esculentum: A Nutrient-Dense Part of Nature

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27.1 INTRODUCTION

Due to rising poverty and demography, the majority of the population in the developed world is struggling to improve living standards and health care delivery. According to estimates, 70–80% of the developing world is reliant on traditional plant-based remedies due to the high cost of pharmaceuticals. From this reality, it can be deduced that by combining data and experimenting, precious, and cost-effective medicaments can be extracted from various plants to meet the needs of an ever-changing world. As a result, the need of medicinal plants cannot be overlooked. There are nearly 1,200 species in the Polygonaceae family of plants. *Fagopyrum* is a genus of 15 species in the Polygonaceae family that are mostly found in the North Temperate Zone (Sanche et al., 2011). The most commonly cultivated species are common Buckwheat (*Fagopyrum esculentum* Moench) and tartary Buckwheat (*Fagopyrum tataricum* Gaertn.) among the major nine agricultural species (Zhang et al., 2012). Buckwheat, a member of this family, can be found almost anywhere but is primarily grown in the northern hemisphere. Buckwheat is a grain grown primarily in Russia and China. Furthermore, in the United

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States, Canada, and Europe, this product is becoming increasingly popular (Li et al., 2001; Stember, 2006).

Despite the fact that *Fagopyrum esculentum* Moench (common buckwheat) has been a minor crop in many countries, it has survived through centuries of civilization and is now grown in nearly every country where cereals are grown. Although the crop is not a cereal, the seeds are often grouped with cereal grains due to their similar uses (Li, 2003). The dehulled groats are boiled as porridge, and the flour is used in the preparation of pancakes, biscuits, noodles, and cereals, among other things. Unlike other cereals, buckwheat protein (BWP) is of high quality and contains a high amount of the essential amino acid lysine (Gimenez-Bastida et al., 2015a). The flowers and green leaves are used to extract rutin for use in medicine, while the small leaves and shoots are used as leafy vegetables. Honey of exceptional quality is produced by this crop (Saturni et al., 2010; Giménez-Bastida et al., 2015b). Consumption of common buckwheat and its enriched products has been linked to a variety of biological and health benefits, including hypocholesterolemia, hypoglycemia, anticancer, antimicrobial, and anti-inflammatory properties. BWPs and phenolic compounds are thought to play a role in these advantages, at least in part (Gonzalez-Sarrías et al., 2013). Some of these effects have been linked to these compounds' antioxidant potential, but recently found mechanisms of action may also be responsible for the observed health benefits (Liu, 2003; D'Archivio et al., 2010). The goal of this chapter is to go over the most recent research on the health benefits of *F. esculentum*, its proteins, and phytochemicals, as well as the mechanisms that underpin the positive effects ascribed to these compounds.

Fagopyrum is a genus of flowering plants of the Polygonaceae family of 15 species primarily found in the North Temperate Zone. Some essential food plants are included, such as *Fagopyrum esculentum* (buckwheat) and *Fagopyrum tataricum* (buckwheat), both of which have similar uses and are classified as pseudo-cereals because they are used in the same way as cereals but do not belong to the Poaceae grass family (Tanja et al., 2015). The Indian subcontinent, most of Indochina, and central and south-eastern China are all home to this genus. Species have been widely introduced in other regions of the world, including the Glacier, Africa, and South America. *Fagopyrum esculentum* is an annual herb with clusters of small pinkish or white flowers and edible triangular seeds, which are consumed as the main buckwheat's worldwide, especially due to their high-quality protein, abundant phenolic compounds, and well-balanced essential amino acids and minerals (Inglett

et al., 2011; Kim et al., 2008). Many people have named *F. esculentum* over the course of its evolution. *Buckwheat er*, common buckwheat *er chi*, and *er ka* were all names used by the ancient Yi people of Yunnan province. *Qi chi er luo* was the name given to common wild buckwheat, while *chi ruo er luo* was given to wild Tartary buckwheat. Buckwheat's various names have been used to trace its migration through Europe and Asia, and they are still used to confirm its origin. In India, common buckwheat is now known as Ogal. Vernacular names are given in Table 27.1 (Al-Snafi, 2017; Qing-Fuchen, 1999). *Fagopyrum esculentum* is a glabrous annual herb that grows up to 1 m tall. Petiolate leaves with ovate-triangular to triangular blades, 2–8 cm long, acuminate tips, and cordate or nearly hastate bases; upper leaves are narrower and sessile. Terminal and axillary inflorescences branch in thick corymbose or paniculate cymes. The achene is triquetrous, with an acute angle and a length of more than 5 mm, more than double the length of the recurrent perianths. The three-sided achenes look like miniature beech tree

TABLE 27.1 Vernacular Names of *F. esculentum*

Hindi	Kotu or Koti
English	Silverhull, Common buckwheat
Assamese	Chutia Lofa, Dhemsi Sak, Dhemsi-sak
Manipuri	Wakha
Dutch	Boekweit
Finland	Tattari
Turkish	Karabuğday
Korean	Memil
Poland	Tatarka gryka or poganka
Russia	Grecicha kul'furnaja
French	ble noir; bouquette; sarrasin; sarrazin
Spanish	Grano sarraceno, Grano turco, alforfón
Portuguese	Trigo sarraceno
Chinese	Qiao mai
Japanese	Soba
Italy	Fagopiro, grano saraceno, sarasin, faggina
Germany	Buchweizen or Heidekorn
Arabic	Al-Hintta Al-Swdaa
Bhutan	Jare
Nepal	Mite phapar
Swedish	Bovete

nuts (*Fagus*). Because of the similarity, the German word "buchweizen" (beech-wheat) was coined, which was later transformed to the current name of buckwheat. Physiochemical parameters showed a foreign matter content of 0.30% and a crude fiber content of 1.44%. The values for total ash, acid insoluble ash, and water-soluble ash were 6.71%, 1.90%, and 3.90%, respectively. The extractive values for alcohol soluble and water-soluble extracts were 65.02 mg/g and 12.71 mg/g, respectively. The swelling index was 0.50 ml/g, and the foaming index was less than 100. The loss due to drying was 4.02% (Neeraj et al., 2020). Several brands of hot and cold breakfast cereals use hulled achenes or groats. Buckwheat flour is used to make "kasha," a nutritious porridge popular in Russia.

Buckwheat is a grain that is just a few years old. It was mentioned for the first time in China in the 5th century. The shattering perennial buckwheat was most likely domesticated in China. Buckwheat has been a valuable subsistence and cash crop in the Himalayan region for over 1,000 years, ranging from northern India to Nepal, Myanmar, Mongolia, China, and Korea. Buckwheat is still very important in these regions, despite the fact that the total area has decreased. In some former Soviet Union republics, it is a common food crop. It is grown in the northernmost parts of Southeast Asia, such as northern Vietnam and northern Thailand, on a sporadic basis. It was introduced into Europe in the early Middle Ages, most likely from Siberia with the Mongols, and quickly became a leading grain crop on poor soils and an important staple food. It became a major food crop in the United States and Canada after being introduced by European emigrants. It is often grown in other parts of the world. However, as chemical fertilizers became more widely used in the early 20th century, the buckwheat region in Europe and North America shrank dramatically, being replaced by higher-yielding crops such as rye, oats, corn, wheat, and Irish potato. Because of its excellent nutritional qualities, it is currently regaining some popularity in Western countries (Al-Snafi, 2017; Anne-Laure et al., 2012).

Buckwheat grain is primarily grown for human consumption and animal feed, but it can also be used as a vegetable, a manure crop, a weed-controlling smother crop, and a source of buckwheat honey. Buckwheat is a popular grain that is eaten in a variety of ways in various countries. Fortunately, buckwheat is currently underappreciated and underutilized as a nutritious food and a viable alternative crop plant, especially in developed countries. Rutin, a medicinal product, is found in the herb. Buck wheat, also known as *Fagopyri herba*, is a rutin-rich plant that has historically been used to make tea to treat hypertonia. Honeybees feed on the nectar produced by the flower.

Buckwheat can be used in a variety of ways in the kitchen. The dehulled grains are boiled and eaten. Flour may be made from whole grains or dehulled grains. The hulls of buckwheat are used to fill a number of upholstered items, including pillows. Straw is an excellent livestock feed. It's always eaten as a noodle soba in Japan. Buckwheat flour is commonly mixed with wheat flour in Europe and North America to make pancakes, biscuits, noodles, cereals, and as a meat extender. Porridge and soup are made with groats and flour in Russia and Poland. It's used to stuff fish in Sweden. Buckwheat is a staple food in many hilly areas of Southeast Asia. Unleavened bread chapattis are made with this flour. It's also fried after being combined with water to make a crispy pakora. Parathas can also be made with the flour and potatoes. It's also used during fasts and spiritual celebrations. Buckwheat is used to make alcoholic beverages, with buckwheat liquor being said to have medicinal properties. Buckwheat is rumored to be used in the manufacture of vinegar in China. In many parts of the Indian subcontinent, buckwheat is grown as a leafy vegetable crop. The plants' tender leafy shoots are harvested and used to make dishes. Buckwheat has long been used by hunters as a food and cover crop for wildlife. Buckwheat is eaten by deer, and they will start foraging as soon as a few seeds have grown. Wild turkeys, pheasants, grouse, waterfowl, and other birds consume the grain. The crop is usually planted but not harvested, so the remaining plants provide food and shelter for wildlife (Al-Snafi, 2017; Anne-Laure et al., 2012; Parminder and Preeti, 2011; Dhakal et al., 2015).

27.2 NUTRITIVE AND BIOCHEMICAL POTENTIAL

Buckwheat is a pseudocereal with high nutritional and nutraceutical properties. Buckwheat is known to be rich in high quality carbohydrates, protein, and amino acid, fatty acid, vitamins, minerals, and bioactive compounds such as polyphenols. However, the total content of components depends on variety or environmental factors. Buckwheat contains abundant mineral elements such as K, P, Cu, Ca, Se, Mg, Ba, B, I, Fe, Pt, Zn, Co as well as cyanide, phytin, and riboflavin (Huda et al., 2021). Buckwheat has a higher concentration of K, Mg, P, Ca, Fe, Zn, Cr, Cu, and Mn than other cereals (Rodríguez et al., 2020). As a result, buckwheat may be a valuable source of microelements like Fe, Mn, and Zn. Furthermore, as compared to other crops, buckwheat has a high bioavailability of Zn, Cu, and K. Mineral distribution in the seed varies depending on the tissues, with mineral concentrations

varying from 2.0 to 2.5% in whole grains, 1.8 to 2.0% in kernels, 2.2 to 3.5% in dehulled grains, 0.8 to 9% in flour, and 3.4 to 4.2% in hulls. It was also asserted that P, K, and Mg are most abundant in bran, and trace elements are abundant in the outer membrane of seeds and seed coat. The embryo, on the other hand, contains valuable essential elements such as Mg, P, S, K, Mn, Fe, and Zn. Buckwheat is the only grain crop known to have antioxidant, anti-inflammatory, and anti-carcinogenic properties due to its high rutin content. Buckwheat has been found to contain more than 130 major polyphenols, in addition to rutin (Christa and Soral-Smietana, 2008). Buckwheat is rich in manganese, phosphorous, and copper. Copper is required for the production of red blood cells. Magnesium relaxes blood vessels leading to the brain and has been shown to help with depression and headaches. Buckwheat is high in folate, which aids in the production and maintenance of new cells, especially red blood cells. It's especially critical for pregnant women to get enough folate. Even if they aren't planning to have children, they should start eating folate-rich foods like Buckwheat. Because buckwheat grains contain more B-complex vitamins, consuming enough folate before and during pregnancy helps to prevent major birth defects affecting the baby's brain (Nepali et al., 2019). Its protein content is high. The total amino acid concentration was 31%. The main amino acids were glutamine, glutamic acid and arginine, apart from that it also contains lysine, histidine, aspartic acid, threonine, serine, proline, half cystine, glycine, alanine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, and tryptophan. It also contains 18% albumin, 43% globulin, 1% prolamine, and 38% gluetin. *Fagopyrum esculentum* protein concentrates and hydrolysate have the ability to be useful as food ingredients. It's also high in dietary fibers, which has a beneficial physiological impact in the gastrointestinal tract and affects the metabolism of other nutrients significantly. Since buckwheat seeds are gluten-free, they are ideal for celiac disease sufferers and buckwheat intake decreases the risk of diabetes due to its high magnesium content (Sayoko and Yoshiko, 1994; Halbrecq et al., 2005; De Francischi et al., 1994). The moisture content of the buckwheat plant (*Fagopyrum esculentum*) and products made from its seeds was 6 to 8%. The lowest moisture content was found in roots (4.3%), while the highest was found in both flours (around 12%). Peels had the lowest amount of crude protein among buckwheat products, at 3.5%. On the other hand, the highest crude protein content of the buckwheat plant was found in the leaves (22.7%) and blossoms (19.1%). Buckwheat seed is packed full of starch, but the amount varies. The starch content of whole grain common buckwheat ranges from 59 to 70% dry matter, but the concentration varies

depending on the method of extraction and cultivar. Amylose content in buckwheat granules ranges from 15 to 52%, with polymerization degrees ranging from 12 to 45 glucose units. Around 0.65–0.76% reducing sugars, 0.79–1.16% oligosaccharides, and 0.1–0.2% non-starchy polysaccharides are also found in buckwheat grains. Sucrose is the most common sugar with a low molecular weight. A small amount of arabinose, xylose, glucose, and the disaccharide melibiose are present. Likewise, the total lipid content of common buckwheat seeds ranges from 1.5 to 3.7%. The embryo has the highest concentration (7–14%), while the hull has the lowest concentration (0.4–0.9%). Total lipids in groats or dehulled buckwheat seeds range from 2.1 to 2.6%, with 81–85% neutral lipids (NLs), 8–11% phospholipids, and 3–55% glycolipids. Palmitic, oleic, linoleic, stearic, linolenic, arachide, behenic, and lignoceric are the major fatty acids found in common buckwheat. The 16 and 18-carbon acids are the most common in all cereals. Long-chain acids such as arachidic, behenic, and lignoceric, which account for about 8% of total acids in buckwheat, are minor components or absent from cereals. Buckwheat had a dry matter content of 60 to 70% in buckwheat products. Whereas peels had the lowest fat content 0.6%. Rutin concentrations were found to be highest in blossoms and leaves, at 83.6 and 69.9 mg per gram, respectively. Buckwheat goods, on the other hand, had the lowest concentration of rutin, with less than 1 mg per gram of dry matter. Best-known buckwheat has a phenolic content of 0.735% to 0.79%. Table 27.2 reflects the average rutin concentration, moisture, starch content, crude protein, and fat content of the buckwheat plant (Petra et al., 2012). Buckwheat includes flavonols, anthocyanins, and C-glucosyl-flavones, three of the several forms of flavonoids (Watanabe, 2007). Buckwheat's leaves, roots, flowers, and fruit contain rutin (quercetin-3-rutinoside), a well-known flavonol diglucoside used to treat vascular disorders. Quercetin (quercetin 3-rhamnoside) and hyperin are two other flavonols that have been identified (quercetin 3-galactoside). The hypocotyls of buckwheat seedlings produce at least three red pigments. One of these is cyanidin, and the other two are considered to be cyanidin glycosides. Vitexin, isovitexin, orientin, and isoorientin are C-glycosylflavones found in buckwheat seedling cotyledons. The hydro benzoic acids, synigic, *p*-hydroxy-benzoic, vanillic, and *p*-coumaric acids are the phenolic acids present in buckwheat seed. Popular buckwheat seeds contain soluble oligomeric condensed tannins, which, together with phenolic acids, provide astrigency and affect the color and nutritional value of buckwheat products (Eggum et al., 1980). N-feruloltyramine and 7-hydroxy-N-feruloyltyramine are found in high concentrations in the roots and at very low levels in other

parts of the plant. Both sections of the plant contain small amounts of protocatechic acid, gentisic-5-O-glucoside, p-hydroxybenzoic acid, p-cumaric acid, and ferulic acid (Parminder and Preeti, 2011). Dry matter, complete digest, protein, fat, fibers, mineral matter, and rutin, isoorientin, and orientin are antioxidants contained in *Fagopyrum esculentum* feed, straw, and green fodder (Dhakal et al., 2015). Table 27.3 demonstrates the nutritional potential of buckwheat based on its biochemical profile.

TABLE 27.2 The Average Rutin Concentration, Moisture, Starch Content, Crude Protein, and Fat Content of *F. esculentum* (Buckwheat) Plants

	Moisture (%)	**Crude Protein (%)**	**Starch (%)**	**Fat (%)**	**Rutin (mg/g)**
Roots	4.3	5.6	0	4.3	3.6
Stalks	7.7	6.5	1.1	2.6	0.5
Leaves	7.5	22.7	6.0	3.1	69.9
Blossoms	6.5	19.1	–	5.7	83.6
Peels	6.1	3.5	57.2	0.6	0.1
Groats	8.3	13.1	69.5	3.4	0.1
Flour	11.5	12.9	67.9	4.1	0.1
Whole Meal Flour	11.9	14.4	61.6	4.1	0.6

TABLE 27.3 Per 100 gm of Buckwheat (*F. esculentum*), Nutritional Potential and Biochemical Value

Principle	**Nutritive Value**
Energy	323–343 kcal
Carbohydrates	59–71.5 g
Total fat	2.4–3.4 g
Saturated fat	741 mg
Monounsaturated fat	0.8–1.04 g
Polyunsaturated fat	1–1.039 g
Omega-3	50–78 mg
Omega-6	961 $mg^{-1}g$
Protein	10.3–13.25 g
Dietary fibers	10 g
Crude fiber	8.6 g
Vitamins	Proportions
Thiamine (B_1)	0.101 mg
Riboflavin (B_2)	0.425 mg

TABLE 27.3 *(Continued)*

Principle	Nutritive Value
Niacin (B_3)	7.02 mg
Pantothenic acid (B_5)	1.233 mg
Vitamin B_6	0.21 mg
Folate (B_9)	30 µg
Tocopherols	4.1 mg
Minerals/Trace Elements	Extents
Calcium	18–64 mg
Iron	2.2–15.5 mg
Sodium	1–16.2 mg
Potassium	460–720 mg
Magnesium	227–231 mg
Manganese	1.3–2.8 mg
Copper	0.17–1.8 mg
Zinc	2–2.4 mg
Selenium	8.3 µg
Phosphorus	347–355 mg

27.3 EXPLORATION OF BIOACTIVE COMPOUNDS AND PHYTOMOLECULES

Polyphenols, alkaloids, terpenoids, steroids, proteins, minerals, condensed tannins, vitamins (B_1, B_2, B_3, B_5, B_6, C, and E), squalene, iminosugars, and phenylpropanoid glycosides are among the constituents of *Fagopyrum esculentum* that have been isolated (Jin-Shuang et al., 2017). Flavonoids in Fagopyrum buckwheat demonstrated remarkable antioxidant and cardio-cerebral vascular protective effects, making these buckwheat's valuable dietary supplements (Watanabe, 1998; Cook and Samman, 1996). Polyphenols, which are biologically active and have a wide range of pharmacological properties such as antibacterial, antivirus, anti-inflammation, and anti-oxidation properties, are one of the most important constituents found in Chinese herbal medicines. The main phenolics compounds present in buckwheat are rutin, quercetin, kaempferol-3-rutinoside, aromadendrin-3-O-D-galactoside, taxifolin-3-O-D-xyloside and a trace quantity of a flavonol triglycoside, which means it has a ton of antioxidant activity. Rutin was not present in cereals or pseudo-cereals, with the exception of buckwheat, which produces the majority of rutin in the inflorescence, stalks,

and upper leaves and can be used as a good source of dietary rutin (Hagels, 1999; Kreft et al., 2006; Watanabe et al., 1997). These buckwheat's also contained catechins (flavanols) and condensed tannins (proanthocyanidins). (–)-Epicatechin, (–)-epicatechin-3-O-p-hydroxybenzoate, (–)-epicatechin-3-O-(3,4-di-O-methyl)-gallate and (+)-catechin-7-O-glucoside were isolated from buckwheat groats (Watanabe, 1998) and (–)-epicatechin-3-O-gallate, procyanidin B-2, and procyanidin B2-3'-O-gallate were found in buckwheat callus and hairy roots (Kalinova et al., 2006). Simultaneously numerous sterols like campesterol, stigmasterol, and sitosterol gift in buckwheat seeds, additionally phytosterols conjointly contained in buckwheat pollen like campesterol, stigmasterol, methylenecholesterol, isofucosterol, cholesterol, brassicasterol, 23-dehydrocampestanol, 7-dehydro-24-methyldesmonstanol, 23-dehydrositosterol, 7-dehydro-24-ethyldesmostanol and sitosterol (Suguru et al., 1989). Buckwheat flowers contain substantial amounts of fluorescent phototoxic compounds such as fagopyrins and protofagopyrins (Eva and Samo, 2015). Allelochemicals in buckwheat include ferulic, caffeic, and chlorogenic acids, as well as fatty acids. Eugenol, coniferyl alcohol, and 3,4,5-trimethoxyphenol were found in buckwheat stems, leaves, and roots (Kalinova et al., 2011). The alkaloids and its derivatives, such as fagomine, 4-piperidone, and 2-piperidinomethanol, were found in above-ground buckwheat sections and had a strong inhibitory effect on lettuce development. (Iqbal et al., 2002). Chemical analysis showed that the plant also contained, cyclitol: (fagopyritol A1, fagopyritol A2, fagopyritol A3, fagopyritol B1, fagopyritol B2, and fagopyritol B3); triterpenoids: (olean-12-en-3-ol and urs-12-en-3-ol); fatty Acids like 6,7-dihydroxy-3,7-dimethyl-octa-2(Z),4(E)-dienoic acid, 6,7-dihydroxy-3,7-dimethyl-octa-2(E), 4(E)-dienoic acid and 4,7-dihydroxy-3,7-dimethyl-octa-2(E), 5(E)-dienoic acid; γ-tocopherol and squalene (Steadmana et al., 2001; Jing et al., 2016; Zheng et al., 2004; Cho et al., 2006). Buckwheat has a distinct flavor and aroma. Different methods were used to extract volatiles from freshly ground buckwheat flour. 2,5-dimethyl-4-hydroxy-3(2H)-furanone, (E,E)-2,4-decadienal, phenylacetaldehyde, 2-methoxy-4-vinylphenol, (E)-2-nonenal, decanal, hexanal, and salicylaldehyde (2-hydroxybenzaldehyde) were the compounds that contributed the most to the buckwheat aroma (Damjan et al., 2009). In addition, when looking for bioactive compounds against human pancreatic cancer cells, Lapathoside A, a phenylpropanoid ester, was isolated and recorded from the roots of buckwheat (Mi et al., 2021). In buckwheat flour, reverse phase high performance liquid chromatography combined with electrospray ionization-time of flight-mass spectrometry was used to isolate

and classify 30 phenolic compounds, including new compounds such as 2-hydroxy-3-O-β-d-glucopyranosil-benzoic acid, 1-O-caffeoyl-6-O-alpha-rhamnopyranosyl-β-glycopyranoside and epicatechin-3-(3″-O-methyl) gallate in buckwheat flour (Verardo et al., 2010). Several flavonols were detected in the embryo, endosperm, testa, and hull of buckwheat using high-performance liquid chromatography (HPLC) photodiode array-mass spectroscopy, including the predominant flavonoid rutin and minor flavonoids like quercetin 3-Orutinoside-3'-O-β-glucopyranoside, kaempferol 3-O-rutinoside, and quercetin (Li et al., 2010b). From buckwheat seed ethanol extract, major constituents such as 9-octadecenamide, n-hexadecanoic acid, ethyl linolate, 9-octadecenoic acid (z), 2,3-dihydroxypropyl ester, ergost-5-en-3-ol (3beta,24R), gamma-sitosterol, lupeol, and fumaric acid were detected by using gas chromatography-mass spectrometry (GC-MS) with electron ionization (Neeraj et al., 2019). Furthermore, Nonanoic acid, (E)-3-hexen-1-ol, and benzothiazole were the main constituents among the 28 identified components, accounting for 92.89% of the total oil of *F. esculentum* were isolated from fresh buckwheat flowers by hydrodistillation and GC-MS method (Jianglin et al., 2018). One of the most important factors in distinguishing honeys from different botanical/floral origins is the presence of volatile organic compounds. Among the identified volatile organic compounds, 3-methylbutanal, butanoic acid, pentanoic acid, and isovaleric acid were significantly higher in the buckwheat honey samples. Other compounds, such as 3-methyl-2-buten-1-ol, 2-butanone, 2-hydroxy-3-pentanone, 4-methylpentanoic acid, 4-pentanoic acid, butanal, 2-methylbutanal, pentanal, dihydro-2-methyl-3(2H)-furanone, 5-methylfurfural, and cis-linalool oxide, were only found in honeys containing buckwheat pollen grains. Buckwheat honey's aromatic and organoleptic properties are attributed to these compounds, which may be considered interesting as potential "variety markers" for botanical determination (Sara et al., 2013). In brief the list of assorted category phytochemicals catalogs in Table 27.4.

27.4 ETHNOMEDICINAL USES AND NATUROPATHIC REMEDIES

Ethnobotanical reports on common buckwheat are scarce. It is considered a healthy food in Japan due to its rutin content. This is said to help increase blood vessel elasticity and thus prevent artery hardening. Traditional folk medicine has used *F. esculentum* for several therapeutic purposes. The leaves of buckwheat are a good source of rutin, which makes it a common

TABLES 27.4 Highlight of Bioactive Compounds Captured in *Fagopyrum esculentum*

Flavonoids	*Flavonols*	Rutin; Kaempferol-3-*O*-sophoroside; Kaempferol-3-O-glucoside-7-*O*-glucoside; Myricetin; Isoquercitrin; Isoquercetin; Quercetin; Quercetin-3-O-β-D-galactoside; Taxifolin-3-*O*-D-xyloside
	Flavones	Luteolin; Vitexin; Isovitexin; Orientin; Isoorientin; Homoorientin
	Flavanones	Hesperetin-7-rutinoside; Hesperetin 7-O-neohesperidoside; Hesperetin-*O*-hexosyl-*O*-hexoside; Hesperetin 5-*O*-glucoside; Hesperetin-*O*-malonylhexoside; Naringenin; Naringenin chalcone; Naringenin-*O*-malonylhexoside; Naringenin 7-O-glucoside; Phloretin; Homoeriodictyol.
	Flavan-3-ol	Catechin; (+)-catechin-7-*O*-glucoside; Epicatechin; Epicatechin-3-*O*-(3,4-di-*O*-methyl)-gallate; (–)-epicatechin-3-*O*-*p*-hydroxybenzoate; Epicatechin gallate; Epiafzelechin-(4–6)-epicatechin; Epiafzelechin-(4-8)-epicatechin-*p*-OH-benzoate; Epiafzelechin-(4-8)-epicatechin-methyl gallate; Epicatechin(4-8)-epicatechin-*O*-(3,4-dimethyl)-gallate; Epiafzelechin-(4-8)-epicatechin(3,4-dimethyl)-gallate; Epiafzelechin-(4-8)-epiafzelechin-(4-8)-epicatechin; Epiafzelechin-(4-8)-epiafzelechin-(4-8)-epicatechin-*O*-(3,4-dimethyl)-gallate.
	Anthocyanins	Cyanidin 3-*O*-glucoside; Cyaniding 3-O-rutinoside; Cyanidin 3-*O*-galactoside; Cyanidin 3-*O*-galactopyranosyl-rhamnoside.
	Flavonolignan	Tricin-4′-*O*-(β-guaiacylglyceryl)-ether-*O*-hexoside; Tricin-7-*O*-β-guaiacylglycerol; Tricin-4′-*O*-β-guaiacylglycerol; Tricin-4′-*O*-syringic acid; Tricin 4′-O-(syringyl alcohol) ether-5-*O*-hexoside; Tricin-4′-O-(syringyl alcohol) ether-7-*O*-hexoside.
Oligomeric Flavonoids	*Proanthocyanidins*	Procyanidin A1; Procyanidin A2; Procyanidin A3; Procyanidin B2; Procyanidin B3; Procyanidin B5.
Isoflavones	6-hydroxydaidzein; 2′-hydroxydaidzein; Sissotrin; Sissotrin; Formononetin; Glycitin; Genistein-7-*O*-glucoside; Formononetin-7-*O*-glucoside	
Fagopyrins	Fagopyrin A; Fagopyrin B; Fagopyrin C; Fagopyrin D; Fagopyrin E; Fagopyrin F	
Alkaloids and Derivatives	Fagomine; 4-piperidone; 2-piperidinomethanol.	

Steroids	23S-methylcholesterol; Stigmast-5-en-3-ol; Stigmast-5,24-dien-3-ol; *Trans*-stigmast-5,22-dien-3-ol; 6-hydroxystigmasta-4,22-dien-3-one; Campesterol, Stigmasterol; Methylenecholesterol; Isofucosterol; Cholesterol; Brassicasterol; Sitosterol; 23-dehydrocampestanol; 7-dehydro-24-methyldesmonstanol; 23-dehydrositosterol; 7-dehydro-24-ethyldesmostanol.
Cyclitol	Fagopyritol A1; Fagopyritol A2; Fagopyritol A3; Fagopyritol B1; Fagopyritol B2; Fagopyritol B3.
Triterpenoids	Olean-12-en-3-ol; Urs-12-en-3-ol; Oleanolic acid.
Stilbenes	Resveratrol
Phenolic Derivatives	Protocatechuic acid; 3,4-dihydroxybenzaldehyde; Chlorogenic acid; Protocatechuic acid.
Vitamins	Thiamine (B_1); Riboflavin (B_2); Niacin (B_3); Pantothenic acid (B_5); Pyridoxine (B_6); Ascorbic acid (C); γ-tocopherol (E).
Fatty Acids	6,7-dihydroxy-3,7-dimethyl-octa-2(Z),4(E)-dienoic acid; 6,7-dihydroxy-3,7-dimethyl-octa-2(E), 4(E)-dienoic acid; 4,7-dihydroxy-3,7-dimethyl-octa-2(E),5(E)-dienoic acid; Pelargonic acid; Caprylic acid; Capric acid; Undecanoic acid; Lauric acid; Palmitic acid.
Volatile Oils/ Liquid	3-Penten-2-one; (E)-3-Hexen-1-ol; (E)-2-Octenal; Pentadecane; (–)-α-Terpineol.
Soluble Carbohydrates	Sucrose; D-chiro-inositol; myo-inositol; galactinol; raffinose; stachyose.
Fatty Alcohol	1-Hexanol; 1-Octanol; Behenyl alcohols; Oleyl alcohols.
Miscellaneous Compounds	(E)-3-Hexen-1-yl acetate; Heptadecane; 5-Methyl-2-furancarboxaldehyde; Benzene acetaldehyde; Octadecane; Tetradecanal; Benzothiazole; Eicosane; Hexadecenal; Isopropyl myristate; Heneicosane; 6,10,14-Trimethyl-2-pentadecanone; Betaine; squalene; n-butyl-β-D-fructopyranoside.

medicinal herb. Rutin dilates blood vessels, decreases capillary permeability, and lowers blood pressure, making it effective in the treatment of a variety of circulatory problems. Internally, the leaves are used to treat high blood pressure, gout, varicose veins, chilblains, radiation exposure, and other ailments. It works best when taken with vitamin C, which helps absorption. It's a specific remedy for hemorrhage into the retina, and it's mostly mixed with lime flowers. A dressing made from the seeds has been used to help nursing mothers get their milk flowing again. The herb has been used to treat erysipelas with an infusion (an acute infectious skin disease). The leaves have been used to produce a homeopathic cure. It is used to treat eczema as well as liver problems. Buckwheat is used in Meghalaya folklore to treat high blood pressure and constipation. It's often used to set bones by

adding a ground-leaf paste (Esser et al., 2021). Colic, choleric diarrhea, and intestinal obstructions are common uses for the seed. Rheumatic pains, lung diseases, and typhoid are treated with root decoction, and urinary problems are treated with root juice. It is used in the treatment of pulmonary sepsis in China. A poultice made from the seeds has been used to help nursing mothers restore their lactation. The herb has been used to treat erysipelas with an infusion (Chakraborty et al., 2009). Seeds have the ability to invigorate the spleen, avoiding food stagnation and descending qi-flowing, according to Traditional Chinese Medicine theory. The therapeutic function of the leaf and stem, according to the Chinese Materia Medicine Dictionary, includes treating choking, ulcers, hemostasis, and bathing wounds. They also report that the book Classified Materia Medica for Emergency indicates that the leaf can be eaten and can improve vision and hearing, as well as keep negative energy at bay. The plant is often used to treat hypertension, which is thought to be due to the fact that the leaf of buckwheat is eaten in rural areas where the incidence is lower (Hu et al., 1992). Buckwheat has been reported to help with stomach problems in Nepal. Because of its medicinal properties, jang, a local buckwheat brew, commands a higher price in some places. Clinical studies on 75 diabetic patients who were given buckwheat biscuits demonstrated a reduction in blood sugar levels. According to other reports from China, buckwheat has a hypoglycemic impact. Currently, buckwheat noodles can be obtained as a diabetes treatment (Wang et al., 1992). It's also mentioned in the British Herbal Pharmacopoeia as an anti-hemorrhagic and hypotensive medication, and it's used in Korean folk medicine for anti-inflammation, detoxification, and fever lowering. Periodontitis and gum bleeding have been confirmed to be treated with *F. esculentum*. Patients who brushed their teeth and gargled with buckwheat flour every morning and evening improved by 62%. Buckwheat was thought to have this effect because it contains several microelements, vitamins, and is particularly high in quercetin and rutin. They claim that these special formulations help to preserve blood capillary resistance by reducing fragility and permeability, preserving, and restoring elasticity, and reducing inflammation (Song and Zhou, 1992). Diarrhea, eczema, multiple eye affections, headache, burning eruptions, pruritus pudenda, sore throat, tonsillitis, uvulitis, nausea, coryza, and leucorrhea have all been treated with *F. esculentum* in homeopathy. This treatment also helped with styes, conjunctivitis, nasal obstruction, burning in the rectum, joint pain, boils, and a productive cough (Allen, 1986).

27.5 TEA-MAKING WITH BUCKWHEAT

It's important to think about how the processing of buckwheat into tea will affect the bioactive compounds in the grain. Making tea from raw buckwheat seeds entails a number of steps. Before being removed from their hulls, raw whole seeds are soaked in water, steamed, and dried. After that, the dehulled groats are roasted to make the tea. The implications of these thermal processing techniques on BWPs are found to be influenced by the buckwheat's lipid content. While lipids can help buckwheat, proteins maintain their thermal stability, they can also cause buckwheat globulins to become disrupted. For the preservation of buckwheat globulins during thermal treatment, it is recommended that a suitable amount of lipids, such as 6.5%, be present (Chuan-He, 2007). Buckwheat tea, also known as Sobacha in Japan, is a beverage made from the roasted grains, leaves, or flowers of the buckwheat plant. Apart from health benefits, tea is enjoyed for fun. In Korea, buckwheat tea is known as memil-cha, and in China, kuqiao-cha. The tea has a light fragrance and a dry, nutty, earthy flavor. Drinking buckwheat tea has many health benefits, including helping in digestion, improving heart health, preventing kidney complications, lowering cancer risk, and encouraging weight loss. When consumed in moderation, buckwheat is not associated with many harmful health effects. Some individuals, however, may be allergic to buckwheat. Treatment with buckwheat herb tea is safe and can have a beneficial effect on patients with chronic venous insufficiency, preventing the formation of edema (Ihme et al., 1996). Similarly, Rutin, quercetin, and C-glucoflavones were also present in the buckwheat hull, but the overall phenolic content was slightly lower than that of green tea leaves. The key flavonoids contained in buckwheat hull tea were rutin and vitexin. As compared to green tea, buckwheat hull tea had lower antioxidant potential and inhibitory activity against the development of fluorescent advanced glycation end products (Zielinska et al., 2013). Further study compared the antioxidant properties of buckwheat after thermal processing such as microwave heating, pressured steam heating, and roasting. The most damaging to the antioxidant properties was found to be pressured steam-heating. These findings suggest that processing methods should be optimized in order to produce buckwheat tea with the highest concentration of beneficial active compounds. Buckwheat tea contains less calories and is therefore an excellent substitute for high-calorie beverages. Buckwheat tea will help you lose weight by replacing high-calorie drinks (Khan et al., 2017).

27.6 PHARMACOLOGICAL PROFILE

Fagopyrum esculentum has significant health benefits due to its well-balanced amino acid sequence and high lysine and arginine content. BWP has been shown to have a wide range of physiological functions, including curing chronic human diseases, reducing blood cholesterin, inhibiting mammary cancer caused by 7,12-Dimethylbenzanthracene, and preventing gallstones, and so many more. In humans, buckwheat consumption is linked to a lower risk of hyperglycemia and enhanced glucose tolerance in diabetics. Furthermore, buckwheat, a globally grown crop, is one of our most significant food sources. It also contains high-value proteins, balanced vitamins, and catechins, in addition to numerous polyphenols. Vitamin E supplementation has been linked to a lower risk of cardiovascular disease, a lower risk of Alzheimer's disease and prostate cancer, a stronger immune system, and a delay in age-related cataracts and macular degeneration.

27.6.1 ANTIOXIDANT EXCELLENCY

F. esculentum contains a variety of antioxidants, including rutin, quercitrin, quercetin, tocopherols, and phenolic acids. The protective effects of ethanolic extracts from buckwheat groats on DNA damage caused by hydroxyl radicals were investigated by some researchers. Under in-vitro conditions, the results showed that 70% of *F. esculentum* can effectively inhibit non-site-specific hydroxyl radical-mediated DNA damage and site-specific hydroxyl radical-mediated DNA strand breaks, implying that *F. esculentum* can be used not only as a readily available source of natural antioxidants but also as an ingredient in functional foods related to prevention and control diseases associated with carcinogenesis. Phenolics are potent antioxidants that help to prevent disease in a variety of ways. Quercetin, rutin, kaempferol, catechins, and other compounds that are abundant in *F. esculentum* are included in this large group. The abundance of phenolic compounds in Fagopyrum buckwheat's leads to their widespread use as a medicinal food (Cai et al., 2006; Bernadetta and Zuzana, 2005). According to this, the antioxidant activity of buckwheat's is influenced by the sum of rutin and total flavonoids present (Jiang et al., 2007). The yield, total phenolics, and antioxidant activity of buckwheat (*F. esculentum*) extracts were significantly affected by different polarity extracting solvents. According to the β-carotene bleaching process, the methanolic extracts had the highest antioxidant activity coefficient (AAC) of 627 ± 40.0 at 200 mg/L and the longest induction time of 7.0 ± 0.2 h, while the acetone extract had the highest scavenging activity of 78.6

± 6.2% at 0.1 mg/mL according to the DPPH method (Sun and Ho, 2005). Furthermore, the ethanolic extract of *F. esculentum* significantly reduced non-site-specific hydroxyl radical-mediated DNA damage and site-specific hydroxyl radical-mediated DNA strand breaks *in vitro*, owing to its strong antioxidant activity (Cao et al., 2008). In DPPH assay and the reducing power method were used to assess the antioxidant capacity of *F. esculentum*. The antioxidant activity of *F. esculentum* was high. At a concentration of 1 mg/ml, the highest antioxidant activity was reported (81.64%) (Abbasi et al., 2015). Buckwheat seed components were extracted from hulls and groats and screened for antioxidant and free radical-scavenging activities using solvents of various polarities. The methanolic extract had the highest level of activity. The radical scavenging effectiveness of extracts was also found to be concentration dependent. Tocopherols were present in the hexane extract, while phenolic acids and flavonoids were abundant in the methanolic extract (Przybylski et al., 1998). Similarly, catechins isolated from *F. esculentum* had higher antioxidant activity than rutin (Watanabe, 1998). In terms of antioxidant and radical scavenging activity, the extract of buckwheat herb was compared to rutin, which was the main constituent of the extract. The reactivity of the antioxidant activity against the 1,1-diphenyl-2-picryl-hydrazyl radical was calculated (DPPH). The extract had significantly higher antioxidant activity than pure rutin in the DPPH assay. Because of the presence of small phenolic compounds in the extract, using the extract from buckwheat herb appears to be more effective than using pure rutin (Hinneburg et al., 2006). Buckwheat hull extract scavenged superoxide anion produced in the xanthine/xanthine oxidase system (IC_{50} = 11.4 µg phenolic compound/ml) and inhibited autoxidation of linoleic acid (IC_{50} = 6.2 µg phenolic compound/ml). Since Buckwheat hull extract significantly improved SOD activity in serum, it was found to extract healthy low-density lipoprotein oxidation caused by Cu^{2+} ion. Buckwheat hull extract has been shown to defend biological systems against oxidative stress in-vitro and to have antioxidant activity in-vivo (Mukoda et al., 2001). Furthermore, Buckwheat honey samples were tested for their ability to inhibit the production of reactive oxygen species (ROS) by activated human PMNs, antioxidant activity (superoxide anion scavenging in a cell-free system), and inhibition of human complement (reducing levels of ROS by limiting formation of complement factors that attract and stimulate PMNs). The majority of the honey samples were found to be active inhibitors of ROS (van den Berg et al., 2008). Likewise, the total phenolic content and antioxidant capacity of the culture and buckwheat dough matrix were assessed. There was an improvement in total

phenolic content. Furthermore, fermented buckwheat's antioxidant ability included an increased percentage of 2,2-diphenyl-2-picrylhydrazyl scavenging activity and ferric decreasing antioxidant power potential (Gandhi and Dey, 2013). Buckwheat phenolic content and antioxidant activity varied across locations, suggesting that increasing conditions and the relationship between variety and climate play an important role in determining individual phenolic and antioxidant properties. However, different processing methods, such as roasting or extrusion, had no discernible effect on the total phenolic content or antioxidant activity of buckwheat flour. Roasted (200°C, 10 min) buckwheat flour only increased in both non-polar and polar compounds, whereas extrusion increased only in polar compounds (Sensoy et al., 2006). When buckwheat flour was suspended in acidified saliva or an acidic buffer solution in the presence of nitrite, proanthocyanidins in the flour reduced nitrous acid output. The nitration and nitrosation of proanthocyanidins may contribute to the scavenging of reactive nitrogen oxide species produced by NO and nitrous acid, and the increase in NO concentration may improve the function of the stomach, assisting in the digestion of ingested foods. Both buckwheat extract and the rutin norm prevented lipid oxidation in mouse brain lipids after digestion in the stomach (Takahama et al., 2010; Kim et al., 2011). Other parts of the buckwheat plant, in addition to the seeds, showed strong antioxidant activity (Watanabe et al., 1997). Hulls, bran, and protein hydrolysates from *F. esculentum* displayed excellent antioxidant activity, including free radical scavenging activity, inhibition of lipid and linoleic acid peroxidation (Christel et al., 2000; Tang et al., 2009; Inglett et al., 2010; Hes et al., 2012). Buckwheat groats, on the other hand, have been shown to have a positive impact on protein and lipid peroxidation (LPO) in rats, as well as an improved lipid profile. As per the researchers, buckwheat groats consumption may protect against dyslipidemia by reducing plasma triglycerides and low-density lipoprotein cholesterol (LDL-C) while improving HDL cholesterol, lowering atherogenicity indexes. Consumption of buckwheat resulted in an increase in antioxidant enzyme activities and antioxidant defense indices, resulting in improved health (Chlopicka et al., 2013).

27.6.2 ANTILIPIDEMIC, HEPATOPROTECTIVE WITH CARDIOVASCULAR RAMIFICATIONS

Buckwheat-rich diets have been related to a reduced risk of high cholesterol and high blood pressure. The Yi people of China eat a buckwheat-rich diet (100 grams per day). Researchers noticed that buckwheat consumption was

linked to lower total serum cholesterol, lower LDL-C, and a high ratio of high-density lipoproteins (HDL) in 805 *Yi Chinese*. Buckwheat also contains a lot of magnesium. This mineral relaxes blood vessels, increasing blood flow and nutrient distribution while lowering blood pressure-the ideal combination for a heart that is healthy. Moreover, Buckwheat's health benefits are attributed in part to its abundance of flavonoids, especially rutin. These compounds assist in maintaining blood flow, avoiding unnecessary blood loss by preventing platelet clotting, and shielding low-density lipoprotein from free radical oxidation into potentially harmful cholesterol oxides. All of these activities aid in the prevention of heart disease. Furthermore, postmenopausal women with elevated cholesterol, high blood pressure, or other symptoms of cardiovascular disease can consume a serving of whole grains, such as buckwheat, at least six days per week (Radhika and Yadav, 2015). Rutin and quercetin were the major phenolics contained in *F. esculentum*. Rutin relaxes smooth muscles and is useful for preventing capillary apoplexy and retinal hemorrhage, as well as reducing blood pressure and demonstrating antioxidant and LPO efficiency. It also has a lipid-lowering effect by reducing dietary cholesterol absorption as well as plasma and hepatic cholesterol levels (Jiang et al., 2007). BWP extract has been shown to have hypocholesterolemia, anti-constipation, and antiobesity properties in rat feeding trials. Furthermore, BWP product decreased cell proliferation, which protected rats from 1,2-dimethyhydrazine (DMH)-induced colon carcinogenesis (Hiroyuki et al., 2006). Likewise, buckwheat (*F. esculentum*) intake in rats minimized numerous cardiovascular risk factors caused by obesity in laboratory rats. For four weeks, the rats were fed an obesogenic diet with buckwheat. The *F. esculentum* group had lower total cholesterol, LDL-C, and HDL levels, as well as a large aortic lumen, all of which decreased cardiovascular risk factors (Son et al., 2008). Angiotensin II-induced hypertrophy in cultured neonatal rat cardiomyocytes was found to be inhibited by buckwheat rutin (Chu et al., 2014). *F. esculentum* was used to isolate and classify an inhibitory peptide for the angiotensin-converting enzyme (ACE). Using a protein sequencing system and electrospray-LC-mass spectrometry, the ACE inhibitor was identified as Gly-Pro-Pro, a tripeptide with an IC_{50} value of 6.25 μg protein/ml (Ma et al., 2006). Different peptides isolated from lactic-fermented buckwheat sprouts were recently reported to inhibit ACE activity in rat thoracic aorta tissue and suppress angiotensin II-mediated vasoconstriction (Masahiro et al., 2014). In a single-center, randomized, double-blind, placebo-controlled clinical trial, the effectiveness of buckwheat herb tea was also determined in patients with

chronic venous insufficiency, and the study documented that the treatment with buckwheat herb tea is safe and has a favorable effect on patients with chronic venous insufficiency, preventing further edema growth (Ihme et al., 1996). In several animal models, BWP induces hypocholesterolemia by increasing fecal excretion of neutral and acidic sterols. The capacity of BWP to disrupt micelle cholesterol solubility through sequestration of cholesterol was investigated. Cholesterol solubility was decreased by 40% when BWP (0.2%) was incubated with cholesterol and micelle lipid components prior to micelle formation. In Caco-2 cells, the reduction in cholesterol absorption was dose-dependent, with maximal reductions at 0.1–0.4% BWP. In cholesterol-binding experiments, an insoluble BWP fraction was correlated with 83% of the cholesterol, suggesting a high cholesterol-binding potential that disrupts solubility and Caco-2 cell uptake (Brandon et al., 2007). Similarly, germinated buckwheat suppresses the gene expression of adipogenic transcription factors like PPAR gamma and C/EBP alpha in hepatocytes, resulting in potent anti-fatty liver effects. BWP is thought to boost health in a variety of ways, including lowering serum cholesterol, preventing gallstones, cancers, and lowering triiodothyronine (T_3) levels (Choi et al., 2007; Koyama et al., 2013; Hiroyuki et al., 2015). Buckwheat and honeyweed supplemented diets have been found to have a positive effect on broiler chick growth rate, and treatment was found to have a strong impact on lowering health-hazardous serum total cholesterol, LDL, triacylglycerols, and elevation of serum HDL cholesterol level, as well as improving blood parameters when compared to commercial regulation (Abedin et al., 2020). After 5 weeks of treatment with both raw buckwheat extract and germinated buckwheat extract, spontaneously hypertensive rats and normotensive Wistar-Kyoto rats showed lower blood pressure and significantly reduced oxidative damage in aortic endothelial cells by reducing nitrotyrosine immunoreactivity in aortic endothelial cells (Kim et al., 2009). In rats fed a high-fat diet, supplementation with a powdered mixture of whole buckwheat leaf and flower, which is high in phenolic compounds and fiber, tended to reduce body weight gain and lower plasma and hepatic lipid concentrations while simultaneously increasing fecal lipids (Lee et al., 2010). Furthermore, rats fed BWP extract for three weeks had substantially lower hepatic triglyceride concentrations and weights of epididymal and perirenal fat pads. Hepatic glucose-6-phosphate dehydrogenase and fatty acid synthase activities were decreased by BWP extract, but hepatic carnitine palmitoyltransferase I activity was unaffected. Moreover, the extract increased fecal excretion of

fat and nitrogen as well as both neutral and acidic steroid (Jun et al., 1996; Tomotake et al., 2008).

27.6.3 F. ESCULENTUM AS CYTOTOXICITY EMISSARIES

When Cellosaurus cell line H22 cells were treated with an extract of *F. esculentum* flowers and leaves, which inhibited tumor cell proliferation and induced apoptosis (Guo et al., 2013a, b). Conversely, by improving the immune function of H22 tumor mice, the immunosuppression induced by cyclophosphamide can be reduced (Guo et al., 2013c). Buckwheat flower and leaf can also help mice avoid developing S180 tumors by raising GSH-Px and Superoxide dismutase activity in the blood and lowering malondialdehyde (MDA) levels (Guo et al., 2012). At a concentration of 1.0 mg/mL, the ethyl acetate (EA) and butanol fractions of *F. esculentum* sprout ethanol extracts inhibited development in A549, AGS, MCF-7, Hep3B, and Colo205 cancer cell lines by 70.3%, 94.8%, 79.6%, 82.3% and 73.2%, respectively (Sun et al., 2012). In addition, in-vitro recombinant buckwheat trypsin inhibitor (rBTI) had potent antiproliferative activity, and its mutant (aBTI) had even greater antiproliferative efficacy against HL-60, EC9706, and HepG2 cells, suggesting that it may be a potential cancer treatment candidate and it also inhibited HL-60 in-vitro (Cao et al., 2008; Tian et al., 2010). Buckwheat consumption was linked to a lower risk of lung cancer in a population-based case-control study (Shen et al., 2008). Buckwheat hull ethanolic extract and its fraction also have anticancer effects against a multitude of cancer cell lines. In sarcoma-180 implanted mice, all extracts at doses of 25 and 50 mg/kg reduced tumor development by more than 20% and 42%, respectively (Kim et al., 2007). Analogously, Lapathoside A, a phenylpropanoid ester isolated from buckwheat roots, has anticancer activity in human pancreatic cancer cell lines (PANC-1 and SNU-213), and treatment with lapathoside A increased apoptosis while affecting the expression levels of apoptotic proteins (Mi et al., 2021). BWP diet significantly reduced cell proliferation and expression of proto-oncogene proteins in the colonic epithelium of rats with Hydrazomethane-induced colon tumors. Dietary BWP reduced the risk of colonic adenocarcinoma by 47% while having no effect on the risk of colonic adenomas (Liu et al., 2001). Dietary BWP also slowed the development of 7,12-dimethyltetraphene-induced mammary carcinogenesis in rats (Kayashita et al., 1999).

27.6.4 THE EFFECT OF F. ESCULENTUM ON MEMORY AND NEURODEGENERATIVE MISERY

The progressive dysfunction and loss of neuronal structure and function that results in neuronal cell death is known as neurodegeneration. Acute neurodegeneration is a disorder in which neurons are quickly weakened and die as a result of a traumatic accident or a sudden insult, such as a head injury, stroke, traumatic brain injury, cerebral or subarachnoid hemorrhage, or ischemic brain damage. Chronic neurodegeneration, on the other hand, is a long-term disease in which neurons in the nervous system undergo a neurodegenerative process that begins progressively and worsens over time due to a number of factors, resulting in the gradual and irreversible death of specific neuron populations. Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis are examples of progressive neurodegenerative disorders (Gao and Hong, 2008). In an in-vitro study, EA, and ethanol extracts of common buckwheat seeds, stems, and aerial components exhibited neuroprotective effects through inhibitory and antioxidant activities of acetylcholisterase, butylcolinesterase, and tyrosinase. These findings indicate that buckwheat has neuroprotective properties. However, it should be noted that in-vivo, nerve cells do not encounter the entire extract. As a result, these in-vitro experiments do not resemble a physiological situation. (Gulpinar et al., 2012). Seed extracts from *F. esculentum* showed significant inhibition of tyrosinase, indicating that seeds may be a promising candidate for Parkinson's disease treatment. Before clinical use, further research into the process should be conducted (Liu et al., 2012). In addition, *F. esculentum* sprouts have a high luteolin content. Since oxidative stress and neuroinflammation are related to the onset and progression of neurodegenerative diseases, as well as neuronal cell death, the researchers found that luteolin reduced oxidative stress in neuroblastoma cells, reduced inflammation in brain tissues, and regulated various cell signaling pathways, meaning that luteolin may be used as a novel therapeutic (Miguel et al., 2008; Nabavi et al., 2015; Zhou et al., 2011). The effects of buckwheat hull extract on toxicant-induced spatial memory impairment and hippocampal neuron damage in rats were also explored. The researchers concluded that supplementing foods with buckwheat hull extract improved rats' spatial memory and protected them from hippocampal neurodegeneration and spatial memory deficiency (Koda et al., 2008). Consequently, the action of buckwheat polyphenol from *F. esculentum* in a repeated cerebral ischemia rat model indicated that buckwheat polyphenol could ameliorate spatial memory impairment by inhibiting glutamate release and delayed NO generation in rats subjected to

repeated cerebral ischemia (Fengling et al., 2004). Similarly, in an eight-arm radial maze, rats consuming common buckwheat (600 mg kg^{1}) dramatically improved the spatial memory impairment caused by scopolamine. The authors exposed primary cultures of rat hippocampal neurons to buckwheat to figure out how it protects them. This extract inhibited cell damage caused by glutamate, kainite, and β-amyloid by scavenging DPPH radicals (Pu et al., 2005).

27.6.5 ANTIDIABETIC AUTHENTICITY

Buckwheat seed intake was found to reduce the incidence of hypertension, dyslipidemia, and hyperglycemia in epidemiological studies (Zhang et al., 2007; Zhang, Li, Li, Yuan, and Wang, 2007). D-chiro-inositol (DCI), flavonoids, and BWP are the key antidiabetic function compounds in buckwheat (Zhang et al., 2011; Yao et al., 2008). Buckwheat's nutrients can help regulate blood sugar levels. Buckwheat groats significantly reduced blood glucose and insulin responses in a test comparing the effect of whole buckwheat groats on blood sugar to bread made from refined wheat flour. The desire to satisfy hunger was also a strong suit for whole buckwheat's (Radhika and Yadav, 2015). It has historically been shown that intragastric administration of a buckwheat concentrate containing DCI, myo-inositol, and fagopyritols dramatically reduced serum glucose concentrations in streptozotocin (STZ) rats in the fed state. DCI is a naturally occurring isomer of inositol and is the key active nutritional component in *F. esculentum* (Kawa et al., 2003). DCI, as an epimer of myoinositol, is thought to be the primary mediator of insulin metabolism, improving insulin action while lowering blood pressure, plasma triglycerides, and glucose levels. As a result, DCI has a lot of interest as an adjunctive therapy for insulin resistance diseases like type 2 diabetes and polycystic ovary syndrome (Fontele et al., 2000; Ueda et al., 2005). Buckwheat intake in the diet can lower blood glucose concentrations and diabetes prevalence rates, according to an experimental study. Normal and type II diabetes rats were given ethanol and water extracts of *F. esculentum* seeds, which significantly reduced blood glucose levels (Lu et al., 2002; Han et al., 2008). The most bioactive constituent of *F. esculentum* flowers and leaves was rutin, which could regulate the metabolic disorder of glucose and lipids in fat emulsion and alloxan-induced diabetic rats and improve insulin resistance and possessed a protective effect on liver injury at an early stage in diabetic rats by decreasing the levels of fasting blood glucose, serum

total bilirubin, alanine aminotransferase and liver index and restoring the histological injury of hepatocytes (Li et al., 2010a, c). Furthermore, BWP decreased blood glucose in alloxan-induced diabetic mice, while pumpkin and buckwheat co-administration significantly reduced blood glucose in alloxan-induced diabetic rats (Liu et al., 2009; Hai and Liu, 2011). Buckwheat also inhibited α-amylase activity in a competitive way, suppressing postprandial hyperglycemia in rats after starch loading. Even after digestion and heating, buckwheat maintained its inhibitory activity against α-amylase. As a result, it is a good candidate for use as a functional component in food for specified health uses, such as foods that help prevent diabetes by lowering blood glucose levels (Kazumi et al., 2018). Buckwheat (*F. esculentum*) has a proteinaceous α-AI albumin fraction that inhibits porcine pancreatic α-amylase (Ikeda et al., 1984). During a six-year study of the impact of whole grains on the incidence of diabetes in Iowa, researchers discovered that women who supplemented the whole grains of *F. esculentum* on a daily basis had a 21% lower risk of diabetes than those who ate one serving per week. Since buckwheat is high in magnesium, it's worth noting that women who consumed the most magnesium-rich foods had a 24% lower risk of diabetes than women who enjoyed the least (van Dam et al., 2002).

27.6.6 RENAL REPERCUSSION

Buckwheat consumption was found to have a significant impact on the relief of diabetes and its complications in clinical trials. In type 2 diabetes mellitus rats, total flavonoids from buckwheat flowers and leaves had a substantial protective effect against kidney damage. In type 2 diabetic rats, total flavonoids from buckwheat flowers and leaves reduced fasting blood glucose, increased insulin resistance, induced creatinine clearance rate and renal morphological alterations, and down-regulated the expression of inhibiting protein tyrosine phosphatase-1B (PTP1B). This effect may be due to inhibiting PTP1B, which lowers blood glucose and reduces kidney damage (Zhao et al., 2011). Similarly, the state of oxidative stress was increased in nephrectomized rats given buckwheat extract by restoring the reduced activities of ROS-scavenging enzymes such as superoxide dismutase and catalase (CAT). The severity of extratubular lesions like crescents and adhesions, the glomerulosclerosis index, and the severity of tubular interstitial lesions all increased as well. Furthermore, buckwheat extracts improved kidney function in nephrectomized rats, as evidenced by lower serum creatinine

levels and a significant decrease in methylguanidine, a uremic toxin derived from creatinine in the presence of hydroxyl radicals (Takako et al., 2002). The kidney injury caused by ischemia-reperfusion in rats is also improved by buckwheat extract. The extract was shown to protect cultured proximal tubule cells exposed to hypoxia-reoxygenation, most likely by prohibiting oxygen free radicals from attacking the cell membranes (Yokozawa et al., 2001).

27.6.7 ANTI-INFLAMMATORY, ANTINOCICEPTIVE, AND ANTIPYRETIC POTENTIAL

Polyphenols and flavonoids abound in buckwheat. Rutin was identified as the most health-promoting antioxidant component and has also been shown to be anti-inflammatory (Liu et al., 2008). Research studies have shown that various extracts of *F. esculentum* are useful for treating or preventing the progression of inflammatory diseases *in vitro* and *in vivo*, demonstrating significant anti-inflammatory activity (Parminder and Preeti, 2011). *In vitro* and *in vivo*, an ethanol extract of *F. esculentum* sprouts showed substantial anti-inflammatory activity. In mice stimulated by lipopolysaccharide (LPS), *F. esculentum* sprouts can decrease the levels of IL-6 and TNF-. Furthermore, it had a direct impact on the expression of IL-6 and IL-8 genes in HeLa cells. *F. esculentum* sprouts, in a global perspective, could be a promising candidate for preventing the progression of various inflammatory diseases (Ishii et al., 2008). Following that, *F. esculentum* was found to be capable of reducing antigen (DNP-HSA)-induced histamine, prostaglandin D2 (PGD2), and cysteinyl leukotriene (cysLT) release in IgE-sensitized RBL-$2H_3$ cells. Consequently, it suppressed antigen-induced HDC2, COX-2, and 5-LO mRNA expression in IgE-sensitized RBL-$2H_3$ cells (Kang, 2012). Additionally, buckwheat was found to have antinociceptive and antipyretic properties (Jing et al., 2016).

27.6.8 ANTIMICROBIAL ACTIVITY

Many bioactive compounds found in plants, herbs, and spices have been shown to have antimicrobial properties and can be used as a source of antimicrobial agents to combat foodborne pathogens. Recent research has found that the volatile oils extracted from *F. esculentum* flowers have antimicrobial activity against seven common bacteria: *Bacillus subtilis*, *Staphylococcus*

aureus, *Proteus mirabillis*, *Agrobacterium tumefaciens*, *Escherichia coli*, *Pseudomonas lachrymans* and *Xanthomonas vesicatoria* (Cabarkapa et al., 2008). In contrast, three new fatty acids were isolated from the methanol extract of *F. esculentum* hulls, and they showed potential antimicrobial activity against *Staphylococcus aureus* and *Enterococcus faecalis* (Cho et al., 2006). Tannins from buckwheat also showed antibacterial activity against *Listeria monocytogenes*, with MICs ranging from 62.5 to 500 microg/ml (Amarowicz et al., 2008). The mycelial growth of *Fusarium oxysporum* and *Mycosphaerella arachidicola* was also inhibited by buckwheat hulls extract (Leung and Ng, 2007). Alternatively, malted extracts of *F. esculentum* endorse that antibacterial agent towards the food borne pathogens (*Streptococcus pyogenes*, *Bacillus cereus*, *Proteus vulgaris*, *Shigella* sp., *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) and might be used as herbal components with their antimicrobial consequences in food industry (Chaturvedi et al., 2013). Concurrently, buckwheat seed supplementation with black cumin seed suppressed pathogenic bacteria such as *E. coli* and *Salmonella* spp. According to these systematic reviews, supplementing broiler rations with 10% buckwheat seed and 1.5% black cumin seed might be an alternative to hazardous synthetic antibiotics for safe poultry production (Islam et al., 2016). Plant defensins are antimicrobial host defense peptides expressed in all higher plants. We highlight a novel antimicrobial peptide (*Fa*-AMP1 and *Fa*-AMP2) isolated from buckwheat seeds using gel filtration, ion-exchange HPLC, and reverse-phase HPLC techniques in this review. This new category of antimicrobial peptides shared characteristics with the defensin and glycine-rich peptide families, as well as having broad antimicrobial activity. Antimicrobial peptides' unique properties as potent antimicrobial compounds suggest that they may have evolved as a sophisticated defense mechanism for protecting the plant body (Fujimura et al., 2003).

27.6.9 ADDITIONAL RELEVANT IMPLEMENTATIONS

F. esculentum, despite the above-mentioned activities, has a multitude of other bioactivities. The central nervous system (CNS) was found to be restrained by *F. esculentum* polysaccharide, which effectively inhibited spontaneous motion, reduced the latent period of falling asleep, and prolonged the sleep time induced by sodium pentobarbital in mice (Lai et al., 2009). Consequently, *F. esculentum* grain extract administered orally, intraperitoneally, or intradermally inhibited compound 48/80-induced vascular permeability

as measured by Evans blue extravasation. Anti-dinitrophenyl IgE-stimulated passive cutaneous anaphylaxis was significantly reduced when buckwheat grain extract was given orally. Compound 48/80-induced histamine release from rat peritoneal mast cells was also inhibited by buckwheat grain extract in-vitro. Furthermore, buckwheat grain extract inhibited the induction of IL-4 and TNF-α mRNA in human leukemia (HL) mast cells by phorbol myristate acetate and A23187. All of these findings point to buckwheat grain extract having an anti-allergic effect in mast cells, most likely by inhibiting histamine release and cytokine gene expression (Kim et al., 2003). According to a recent study, *F. esculentum* can be used as a nematicidal plant to combat root knot nematodes and can be integrated into pest management systems. Interestingly, a methanolic extract of the dried plant showed anthelmintic activity with EC_{50} values of 62.6 and 40.8 µg/ml after 48 and 72 hours of immersion, respectively. However, after the same time of immersion, the extract from fresh plant was less active, with EC_{50} values of 127.7 and 98.3 µg/ml, respectively (Aissani et al., 2018). The extraordinary benefits of a honeybee and *F. esculentum* grains powder ointment in the treatment of a large dermal wound in a male rabbit accidentally injured. The ointment's beneficial effects were observed in the inflammatory phase, wound contraction stimulation, and a reduction in healing time. The ointment of honey and buckwheat, according to the report, stimulates the healing process in dermal wounds, specifically in terms of wound contraction, because it contains significant quantities of nutrients, including essential amino acids like lysine, proline, and glycine, as well as vitamin C, all of which are involved in the formation of collagen synthesis precursors (Zouhir, 2014). The prevalence of skin cancer has increased dramatically in recent years. Sunlight, particularly ultraviolet radiation, is thought to be a key factor in the development of skin cancer. As a result, there is a growing interest in developing UV-protective compounds for use in sun care products. Topical application of herbal antioxidants is one method. A commercial UV absorber was compared to the photoprotective properties of buckwheat herb extract. The inhibition of photosensitized LPO of linolic acid was used to test the photoprotective properties of buckwheat extract. The extract was more effective than rutin or a commercial UV absorber at preventing linolic acid peroxidation caused by UV light. Because of the presence of minor phenolic compounds in the extract, using the extract from buckwheat herb was more useful than using pure rutin (Hinneburg et al., 2006). Furthermore, various Buckwheat-derived products have been documented and shown to have health benefits, including prebiotic, antifatigue, immunomodulation, leg edema protection, and stomach

activity improvement (Giménez-Bastida and Zieliński, 2015; Prestamo et al., 2003; Ihme et al., 1996). Silver nanoparticles stabilized by *F. esculentum* starch have been reported as a promising antimicrobial agent against bacteria and fungi. The nanoparticles inhibited Gram-negative bacteria (*Escherichia coli*) more effectively than Gram-positive bacteria (*Staphylococcus aureus*) (Phirange and Sabharwal, 2019). In addition, *F. esculentum* leaf extract also aids in the green synthesis of biocompatible gold nanoparticles, suggesting that organic biomolecules on the surface of the gold nanoparticles have cytotoxicity activity against human HeLa, MCF-7, and IMR-32 cancer cell lines. The gold nanoparticles were also found to be non-toxic and have potential for use in a variety of biomedical applications (Babu et al., 2011). The effect of copper and silver nanoparticles on somatic cells of *F. esculentu*m was recently studied. It was concluded that copper nanoparticles are more cytotoxic than silver nanoparticles based on the findings. At the same time, lower concentration of nanoparticles are beneficial to plants, while higher concentrations cause chromosomal aberrations (Kumar et al., 2020).

27.7 FORTHCOMING PROBABILITY

Although it's an underutilized crop, common buckwheat (*Fagopyrum esculentum*) has numerous benefits for both growers and consumers. *F. esculentum*, with its high lysine content, is a highly desirable crop in areas where transportation and protein sources are scarce. A healthy amino acid profile can be achieved by combining it with cereal grains that are low in lysine. Because this is a highly beneficial trait of the species, few crop development efforts have concentrated on growing lysine or other amino acid content. In some collections, the amino acid content of accessions has been evaluated, but no evaluation of related species has been done to date. It's possible that there's a lot of diversity out there that could be used to help the species grow. We summarized the current phytochemical and pharmacological research on *F. esculentum* in this chapter. Modern pharmacological studies have validated almost all of their common applications, focusing on their anti-tumor, antioxidant, anti-inflammatory, hepatoprotective, antidiabetic, antibacterial, antiallergic, antifatigue, and other activities. A large number of studies on the chemical profile of these *F. esculentum* have been conducted due to their flexible pharmacological properties. Flavonoids, phenolics, fagopyritols, triterpenoids, steroids, and fatty acids were among the compounds isolated and described. Flavonoids

and phenolic compounds were thought to be the most active elements, responsible for the majority of their functions. There are few published reports on therapeutic effectiveness, toxicity, or side effects of *F. esculentum* and its constituents due to a lack of clinical trials. To confirm the effectiveness and safety, large-scale, well-controlled, and double-blind clinical trials are urgently required. Better descriptions of the mechanisms of action of various extracts and compounds are needed, as well as a demonstration of the potential interactions between bioactive constituents and synthetic drugs. Consequently, before these bioactive compounds are used in clinical practice, the structure–activity relationship and potential synergistic effect among them must be fully understood. Future research should also focus on epidemiological studies and the consolidation of mechanisms of action, especially in humans. These studies would provide a useful framework for incorporating this pseudocereal into the development of novel and nutritious foods, as well as increasing its use.

KEYWORDS

- **angiotensin-converting enzyme**
- **antioxidant activity coefficient**
- **buckwheat**
- ***Fagopyrum esculentum***
- **high-density lipoproteins**
- **lysine**
- **reactive oxygen species**

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CHAPTER 28

Star Anise (*Illicium verum* Hook. f.): A Systematic Review on Its Traditional uses, Bioactive Resources, and Pharmacological Properties

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28.1 INTRODUCTION

Illicium verum Hook. f. (Syn: *Illicium stellatum* Makino) belongs to the family Schisandraceae (POWO, 2019). The plant is commonly called Star anise, Chinese star anise, Sternanis, Badiane, Bunga lawing, Sonf, Anise etoile, Chakramoggu, and Anasphal, etc. (www.flowersofindia.net; Wang et al., 2011).

It is a medium sized evergreen tree, growing up to 15 meters tall. Leaves coriaceous, ventral side pubescent, aromatic, simple, lanceolate, elliptic or elliptic obovate, 5–15 cm × 2–5 cm, apex acute. Flowers bisexual, solitary, subterminal or axillary, pink to dark red in color, peduncle 1.5–4 cm; spirally arranged perianth lobes 7 to 12. Stamens 11–20, spirally arranged with thick short filaments. Fruit star-shaped follicetum, reddish-brown, with six to eight

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boat-shaped follicles arranged in a whorl. Follicle 1–2 cm in length, rough, and rigid, reddish-brown colored with one seed each. The ripened follicle hard and wrinkled, open along the ventral edge. Seeds ovoid, smooth, shiny, and brittle, brown colored, approximately 8–9 × 6 mm. The plant is native to North-East Vietnam, South-West China and introduced to India, Cambodia, and China South-Central (POWO, 2019; Wang et al., 2011).

The name of genus *Illicium* is derived from the Latin word '*illicere allure,*' probably due to its sweet and striking fragrance (Wang et al., 2011). The characteristically shaped fruit of Star anise is an important spice and recorded in a Chinese herbal classic treatise, the Compendium of *Materia Medica* (Bencaogangmu), in Ming Dynasty. Chinese Pharmacopoeia (2010th edition) stated the properties of the plant fruit as warming yang and used to treat skin inflammation, rheumatism, vomiting, insomnia, and stomach ache (Itoigawa et al., 2004). In the 17th century, fruit was first introduced into Europe as a famous spice with its distinctive licorice taste which is due to its chemical compound, anethole. Fruit powder is also used in traditional medicine as a sedative and in the treatment of nervousness and sleeplessness (Wang et al., 2011). The essential oil extracted from star anise fruits are used as an antiseptic and applied topically to treat rheumatism and as an antidote for several poisons (Chin and Keng, 1990; Verghese, 1988). In India and Japan, both fruits and essential oil are used as carminative and stomachic (Ilyas, 1980; Namba and Tuda, 1993). In Indonesia and Malaysia, the Medicinal Herbs Index and the Dictionary of the Economic Products mentions its therapeutic uses as an external application for insomnia and to ease the childbirth (Kasahara and Hemmi, 1995). In Malaysian treatise, A Dictionary of the Economic Products illustrated the similar therapeutic applications in the local communities of Malaysia (Burkill, 1966). It is also one of the most frequently used medicinal plants to alleviate colitis in babies and stomach aches in Mexico and the United States. Whereas in Eastern Cuba, the carminative herbal mixtures contain certain species of *Illicium* used to treat gastro-intestinal problems (Cano and Volpato, 2004).

Star anise is extensively used in Indian, Chinese, Indonesian, and Malaysian cuisines and it is one of the major ingredients of Chinese spices along with fennel seeds, cloves, sichuan pepper, and cinnamon. It is generally used in chicken and pork dishes in China and chewed after a meal as mouth freshener (POWO, 2019). It is also used to flavor the Thai iced tea, to enhance the flavor of meat and in making '*Pho bo soup,*' a Vietnamese noodle soup. Fruits are used as a spice in the preparation of many stews and curries such as *biryani* and *masala chai* throughout the Indian subcontinent (Wang et

al., 2011). The powdered plant bark is used as incense and the essential oil isolated from star anise fruits are used in making soaps, perfumes, and toothpaste. It is also used in the preparation of alcoholic beverages *viz*. pastis, sambuca, and some types of absinthe. The plant used as an ingredient in the preparation of anise-flavored liqueurs, the best being *anisette* and *liqueur Galliano*. In addition, the bark powder is also used in baking and as a cheaper substitute for star anise in making mulled wine (POWO, 2019; Wang et al., 2011).

28.2 BIOACTIVES

Li et al. (2016) analyzed the chemical constituents of petroleum ether (PE), ethyl acetate (EA) and methanol (MA) fruit extracts of *I. verum* through GC-MS technique. Among all, 44 compounds with more than 0.20% concentration were identified from PE, EA, and MA extracts. The compound trans-anethole was found as the major component, with 72.25% composition in PE, followed by EA (52.54%) and MA (41.14%). Similarities in the composition of chemical constituents were reported, except for some minor components. The compounds 4-ethyl benzaldehyde and 1-(4-methoxyphenyl)-2-propanone were reported with 3.40 and 3.68% in MA extract. Similarly, EA extract showed higher proportions of 1-(3-methyl-2-butenoxy)-4-(1-propenyl) benzene (6.22%), cis-3,5-dimethoxy-β-methyl-β-nitrostyrene (4.24%), hexadecanoic acid (4.07%) and benzyl alcohol (4.04%). Moreover, even PE extract showed higher 1-(3-methyl-2-butenoxy)-4-(1-propenyl) benzene (4.73%) and benzyl alcohol (2.81%) (Li et al., 2016).

Qin et al. (2007) analyzed the influence of three different essential oil extraction methods on the volatile components of *I. verum*. The chemical composition of oil samples extracted through supercritical fluid extraction (SFE), steam distillation (SD) and solvent extraction (SE) methods were analyzed by GC-MS technique. The quality parameters of the oil extracted from the SFE method was close to that of SD and SE. Even if the extraction yield in SFE (9.2%) was very close to SE (9.3%), it was still higher than that of SD (8.2%). The sensory evaluations such as odor and taste of the oils from SFE and SE were usually more vivid and natural than that of SD. Analysis revealed the significant differences in the composition of volatile oil extracted from SD and oleoresins through SFE and SE methods. Comparative account of volatiles and fatty acid compositions of oil samples revealed that some of the compounds are with high relative peak area percentage, such as limonene (1.94, 0.49, 1.57%); linalool (1.67, 0.63, 0.45%); allylbenzylether (1.75,

3.11, 2.43%); propanal, 2-methyl-3-phenyl (0.98, 1.64, 1.25%); estragole (5.15, 3.56, 1.71%); anisaldehyde (1.77, 0.9, 1.27%) and trans-anethole (74.96, 70.61, 77.31%) in SD, SE, and SFE, respectively.

Peng et al. (2014) identified 18 compounds from *I. verum* oil. Major volatiles with higher peak area percentage were trans-anethole (94.8%), followed by 1-(3-methyl-2-butenoxy)-4-(1-propenyl) benzene (3.2%), estragole (0.4%), linalool (0.3%), limonene (0.3%), 4-terpineol (0.18%), α-pinene (0.03%) and 1,8-cineole (0.01%). Further, Wu et al. (2015) chromatographed the aqueous ethanolic extract of plant fruits and found a new compound, illiciumflavane acid (1); along with 13 known compounds (2–14). Authors reported quercetin (2); 3′-methoxy quercetin (3); 3′,4′-dimethoxy quercetin (4); (E)-1,2-bis(4-methoxyphenyl)ethene (5); 4-methoxy cinnamic acid (6); (1R,2S)-1-(4′-methoxyphenyl)-propanediol (7); 4-methoxy-2-(E)-propenylphenyl-β-D-glucopyranoside (8); 3-hydroxy-4-methoxy benzoic acid (9); *p*-hydroxy benzoic acid (10); 2,4-dihydroxy benzoic acid (11); gallic acid (12); *p*-methoxy benzoic acid (13); and (3R,4R,6S)-3,4,6-trihydroxycyclohex-1-enecarboxylic acid (14). Recently, Li et al. (2020) have also analyzed the essential oil of the plant and reported the major components trans-anethole (91.32%), D-limonene (2.0%) and estragole (2.0%) (Figure 28.1).

28.3 PHARMACOLOGY

28.3.1 ANTICANCER ACTIVITY

Asif et al. (2016) investigated *in vitro* cytotoxic activity of essential oils (EOs) obtained from the ethanol extract of fruits against human colon cancer cell lines, HCT 116 (ATCC CCL-247) and HT-29 (ATCC HTB-38) through MTT assay using fluorescent dyes. The test samples of EO (25, 50, and 90 μg/mL), the positive control 5-Fluorouracil (5-FU, 5 μg/mL) and the negative control (0.5% dimethyl sulfoxide in media) were used to determine the anti-metastatic properties through Matrigel invasion, cell migration and colony formation assays. The greater cytotoxic potentiality of EO was found against HCT 116 (IC_{50} 50.34 ± 1.19 μg/mL). Meanwhile, the dose-responsive reduction in mitochondrial membrane potential, distinct nuclear morphological changes, followed by cell invasion, migration, and colony formations were observed in the EO treated cells. The study also depicted the dose dependent criterion in the condensation of chromatin fibers and characteristic crescent-shaped nuclei in the treated cells. After 24 hours of treatment with 25, 50, and 90 μg/mL of EO and 5-FU (5 μg/mL), the apoptotic indices were 12.55

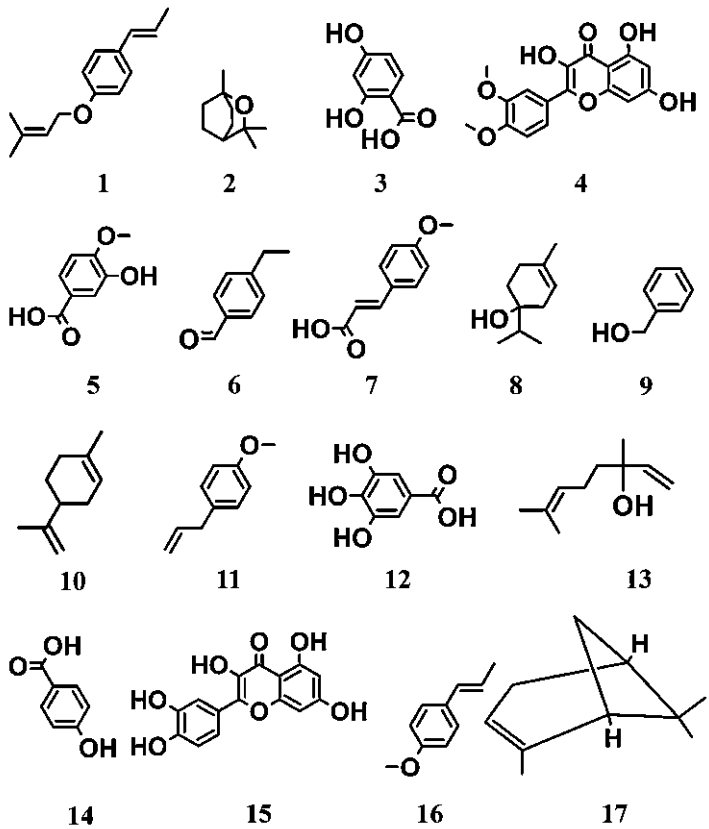


FIGURE 28.1 Structures of 1-(3-methyl-2-butenoxy)-4-(1-propenyl) benzene (1); 1,8-cineole (2); 2,4-dihydroxy benzoic acid (3); 3′,4′-dimethoxy quercetin (4); 3-hydroxy-4-methoxy benzoic acid (5); 4-ethyl benzaldehyde (6); 4-methoxy cinnamic acid (7); 4-terpineol (8); benzyl alcohol (9); D-limonene (10); estragole (11); gallic acid (12); linalool (13); *p*-hydroxy benzoic acid (14); quercetin (15); trans-anethole (16); and α-pinene (17).

± 2.77, 39.26 ± 11.69, 54.06 ± 10.69, and 77.31 ± 12.01% respectively and were significantly high as compared to the untreated cells (3.07 ± 5.69%), especially at higher doses. At 25, 50, and 90 μg/mL, a significant inhibition of wound closure was observed (10.01 ± 3.44%; 23.12 ± 3.05% and 46.09 ± 3.32%, respectively), while in the 5-FU treated group, 81.40 ± 9.09% inhibition of wound closure was observed, i.e., after 24 hours. The experiment was stopped when the gap in negative control (media with 0.5% DMSO) was closed, i.e., after 24 hours. A modified Boyden chamber method was employed to study the efficacy of EO on the invasion of tumor cells through Matrigel basement membrane. At the concentration of 25, 50, and 90 μg/mL

of EO, the cell invasion inhibition percentage was 33.33 ± 7.43, 55.01 ± 3.67, and 60.30 ± 6.73%, respectively, which was significantly higher than control group. Similarly, the colonization inhibition percentage of EO at 25, 50, and 90 μg/mL was 17.66% ± 2.63%, 37.87% ± 1.66% and 80.7% ± 19.2%, respectively. In the positive control group (5-FU-treated wells), 5% survival rate and 98.70% ± 2.80% colonization inhibition were also observed. The potential cytotoxic effect of *I. verum* EO could be due to the inhibition of key steps in the metastatic process and induction of apoptosis (Asif et al., 2016).

28.3.2 ANTIMICROBIAL ACTIVITY

The essential oil of star anise fruit was screened for antifungal activity against post-harvest pathogens such as *Pythium aphanidermatum* and *Botryodiplodia theobromae* (Huang et al., 2010). The crude essential oil at 0.5 mg/mL concentration inhibited *P. aphanidermatum* mycelial growth, at the rate of 93.82%, after four days of exposure. The compound trans-anethole at the same concentration greatly inhibited the mycelial growth. The IC_{50} values of crude oil and trans-anethole were recorded as 0.23 and 0.20 mg/mL, respectively. It was also found that after six days of exposure, both *I. verum* crude essential oil and trans-anethole in medium (0.5 mg/mL each) inhibited the mycelial growth of *B. theobromae* by 68.20% and 83.04% with IC_{50} of 0.34 and 0.27 mg/mL, respectively. The inhibitory effect of crude essential oil and trans-anethole on spore germination of *Magnaporthe oryzae* was also studied and inhibition was found to be 58.40–92.50% and 53.50–83.50%, respectively. Further, Yang et al. (2010) carried out antibacterial activity of supercritical CO_2 and ethanol extracts of *I. verum* against 20 clinical isolates of *Pseudomonas aeruginosa*, 20 of methicillin-resistant *Staphylococcus aureus* and 27 of *Acinetobacter baumannii*. Diethyl ether fractions from both the extracts revealed substantial antimicrobial activity with MIC values ranging between 0.15, 0.70, and 0.11 mg/mL, respectively.

Li et al. (2020) investigated the antifungal properties of *I. verum* essential oil against *Aspergillus flavus* to establish its use in the preservation of lotus seeds. The essential oil exhibited strong inhibitory effects with minimum inhibitory concentration and minimum fungicidal concentration (MFC) of 2.0 and 4.0 μL/mL, respectively. It also exhibited the inhibitory effects on mycelial growth, production of spores, biosynthesis of aflatoxin B1 and B2 at 3.6 μL/mL concentration. It completely inhibited the production of aflatoxin B1 and B2 at the concentrations above 6.0 μL/g and demonstrated

its efficacy as a potent biological fumigant in preserving the lotus seeds (Li et al., 2020).

Recently, Eveline and Novita (2020) performed antimicrobial activity of crude acetone and ethanol extracts [10, 20, 30, 40, and 50% dilutions (w/v)] against three food spoiling bacteria (*Staphylococcus aureus*, *Escherichia coli*, and *Bacillus cereus*) through well diffusion method. The ethanol extract (30%) found potent, with more than 6 mm diameter inhibition zone, followed by MIC and MBC values of 1.59 and 6.36% for *S. aureus*, 1.04 and 4.18% for *E. coli* and 0.59 and 2.39% for *B. cereus*, respectively. Terpenoids [anethole; β-caryophyllene; β-bisabolene and 2,6-dimethyl-6-(4-50 methyl-3-pentenyl)-2-norpinene] were identified as major antibacterial compounds in the extract. However, the fatty acid compounds (stearic acid, 6-octadecenoic acid, and hexadecanoic acid) and benzaldehyde (4-anisaldehyde, p-allylanisole) were found to be less active.

28.3.3 APHICIDAL ACTIVITY

Li et al. (2016) and Zhou et al. (2016) performed aphicidal activity and the underlying mechanism of *I. verum* PE, EA, and methyl alcohol (MA) fruit extracts against *Myzus persicae*. Acetyl-cholinesterase (AChE) and glutathione S-transferases (GSTs) activities of *M. persicae* strain were also tested after the contact treatment. The results of both the studies showed 74.46, 89.95, and 68.93% mortalities in PE, EA, and MA extracts, respectively, followed by IC_{50} of 0.27, 0.14, and 0.31 mg/L at 1.0 mg/L concentration in respective extracts. More than 50% inhibition of AChE and GSTs activities were noted in *M. persicae*, after 72 hours treatment with the extracts.

28.3.4 ANTIOXIDANT ACTIVITY

The antioxidant activity of ambient water extract (ATWE) and boiling water extract (BWE) of star anise were evaluated for lipid peroxide inhibitory, hydroxyl radical scavenging, DPPH (1,1-diphenyl-2-picryhydrazyl), superoxide radical scavenging and DNA damage protectant activities (Dinesha et al., 2014). The extracts at 25 µg exhibited 37 and 39% inhibition of malondialdehyde (MDA) formation by scavenging $OH\cdot$ radicals. Whereas the positive standards, i.e., butylated hydroxy anisole, α-tocopherol and curcumin inhibited the hydroxyl radicals by 82, 78, and 85% at 400 µM concentrations. Further, nitro blue tetrazolium assay was also carried out

for investigating the superoxide scavenging activity of ATWE and BWE. The extracts showed 41% and 48% inhibitions, respectively, whereas, the standard ascorbic acid, α-tocopherol and curcumin showed 55, 61, and 51% inhibition, respectively at 400 μM concentration.

Luis et al. (2019) analyzed the antioxidant potential of essential oil from ripened seeds of *I. verum*, which showed strong DPPH radical scavenging activity (IC_{50} 3.46%; antioxidant activity index 1.02). The capacity of the essential oil to inhibit lipid peroxidation (LPO) was measured by the β-carotene bleaching assay and was significantly lower (IC_{50} 0.28%) than that of butylated hydroxytoluene (IC_{50} 3.58%). The EA extract of fruit and its fractions exhibited a remarkable DPPH radical scavenging activity with IC_{50} of 57.43 and 38.60 ppm, respectively (Yang et al., 2012). Similarly, ABTS+ radical scavenging activity of ethanol, hexane, ethyl ether, chloroform, EA, and aqueous fractions were 15.82, 0.12, 26.75, 25.73, 26.95, and 18.24 mmol trolox/100 g DW, respectively. Results indicated the capability of ethyl ether and EA fractions in scavenging the free radicals *via* an electron or hydrogen donating mechanisms.

28.3.5 ANTICHOLINESTERASE (ACHE) AND BUTYRYLCHOLINESTERASE (BCHE) INHIBITORY ACTIVITIES

AChE and BChE inhibitory activities of hydroethanolic (70:30) extract, its fractions and essential oil extracted from dried fruit powder were studied. The pure compound anethole from essential oil showed significant activities (IC_{50} 39.89 ± 0.32 and 75.35 ± 1.47 μg/mL for AChE and BChE, respectively), while in the crude essential oil, the IC_{50} was 36.00 ± 0.44 μg/mL and 70.65 ± 0.96 μg/mL for AChE and BChE, respectively. Similarly, hydroethanolic extract showed appreciable AChE and BChE activities with IC_{50} 91.84 ± 1.29 and 58.67 ± 0.16 μg/mL, respectively (Bhadra et al., 2011).

28.3.6 CENTRAL NERVOUS SYSTEM (CNS) ACTIVITY

Chouksey et al. (2013) evaluated the acute toxicity of n-hexane, EA, and methanolic fruit extracts and their effects on the central nervous system (CNS). The activity was evaluated based on the parameters of general behavior, locomotor activity, anxiety, sleeping pattern and myocoordination activities in the treated animals. The extract was found toxic at

2,000 mg/kg body weight, whereas its 1/10 fraction proved to be suitable therapeutically. The treatment dose of all the extracts (200 mg) through intraperitoneal injection caused moderate to slight depression in general behavior, significant depression in the locomotory activity, increased sleeping time and produced profound anxiolytic effects in the extract treated animals.

28.3.7 COAGULATION STUDIES

Sayyar et al. (2020) studied the effects of methanol extract (150–350 mg/kg dose) on different coagulation parameters *viz*. prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT) in rabbits. The administration of methanol extract (250 mg) for 30 days resulted in elevation of PT, aPTT, and TT. However, the administration of the extract for 60 days at 250 mg/kg resulted in a significant increase in PT (14.13 ± 0.35 seconds) and aPTT (27.06 ± 0.81 seconds) in contrast to TT. Administration of MEIV for 30 days at 350 mg/kg also caused noteworthy elevation in PT (15.01 ± 0.23 seconds) and aPTT (32.38 ± 0.21 seconds) as compared to the control animals.

KEYWORDS

- **anethole**
- **essential oils**
- **glutathione S-transferases**
- ***Illicium verum***
- **methanolic fruit extracts**
- **star anise**
- **steam distillation**
- **supercritical fluid extraction**

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CHAPTER 29

Leptadenia reticulata (Retz.) Wight & Arn.: A Review on Pharmacological Properties and Bioacitves

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29.1 INTRODUCTION

Leptadenia reticulata (Retz.) Wight & Arn. belongs to the family Apocynaceae. *Cynanchum reticulatum* Retz., *Asclepias javanica* Burm. *ex* Decne., *Leptadenia brevipes* Wight ex Hook.f., *Leptadenia appendiculata* Decne. and *Leptadenia imberbis* Wight are the synonyms for this species (POWO, 2019). Common names of this plant are Jivanthi, Dhori, Bugudi Hoovina Gedde, Cork Swallow Wort, Guttipaala, Paalai Keerai, etc.

It is a twining shrub with milky latex. Stem with deeply cracked cork-like bark. Leaves leathery, broadly ovate, truncate base or superficially cordate with pointed apex, hairless above, velvety hairy below. Flowers greenish-yellow, in lateral or sub-axillary cymes, often pubescent; peduncle 0.5 cm long, pubescent; hairy bracts; calyx cupular, up to 2 mm, ovate; corolla tube up to 1.5 mm, lobes up to 3 mm, triangular-ovate, margins folded, pubescent;

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ovary 1 mm. Follicles paired, woody, bluntly acute at both ends. The plant is native to Sri Lanka, Nepal, Myanmar, Bangladesh, and India. The distribution in India is mainly recorded in the sub-Himalayan tracts of the Punjab, Uttarakhand, and throughout the Deccan peninsular region up to range of altitude of 900 m. It is also distributed throughout Mauritius and Madagascar (POWO, 2019; www.flowersofindia.net).

The old Indian treatise 'Atharva Veda' (4500–1600 BC) mentioned its therapeutic uses as a stimulant and tonic. *Charaka* and *Vagbhata* described that it as a significant *Rasayana* medicine, which maintain health, vigor, fitness, strength, improves tone of voice, cures eye diseases like night blindness, fever, and cough. It is used in the preparation of '*Chyawanprash*' due to its curative characteristics. It is a very good medicine for the treatment of prolapsed uterus, as eye tonic, stimulant, galactagog, diuretic, and astringent. The Bhil tribes of Southern Rajasthan consume its leaves and root paste in water to treat gangrene. It is also used for treating ear and nose disorders, emaciation, asthma, skin infections such as wounds and ringworm (Sneha et al., 2016a; Dhalani and Nariya, 2017; Godara et al., 2019).

29.2 BIOACTIVES

L. reticulata is one of the important traditional medicinal plants, frequently used to treat various disorders *viz*. dyspnea, cough, tuberculosis, cancer, dysentery, emaciation, burning sensation, night blindness, hematopoiesis, and fever. The therapeutic potential of the herb is due to several bioactive constituents such as ferulic acid, luteolin, diosmetin, rutin, α-amyrin, β-amyrin, stigmasterol, hentricontanol, β-sitosterol, a triterpene alcohol simiarenol, reticulin, apigenin, leptaculatin, and deniculatin which exhibit anticancer, antibacterial, antioxidant, lactogenic, anti-asthmatic, anti-implantation, modulating, antifungal, hepatoprotective, antidiabetic, and anti-inflammatory activities (Dhalani and Nariya, 2017; Mohanty et al., 2017). It is used in the treatment of fever, emaciation, tuberculosis, cardiac ailments, and hemorrhage because of its galactagog, stimulant, and restorative properties. Its constituents like β-sitosterol, β-amyrin, leptadenol, and alkaloids jibentin α and β-jivantic acids rejuvenates and nourishes the body, increases longevity, immune modulation, memory, and adoption (Dhawan et al., 2013).

Godara et al. (2019) carried out comparative profiling of phytoconstituents from ethyl acetate (EA) and methanol extracts using GC-MS. The

shade dried leaves, stem, root, and the leaf derived callus were sequentially extracted with methanol and EA solvents. The extracts were further subjected to GC-MS analysis and 77 major phytochemical compounds were detected. GC-MS analysis of leaf extract in methanol and EA indicated the presence of 31 and 22 compounds, respectively. The major compounds recorded were 1-tridecene (23.73%), phytol acetate (13.90%), [6-hydroxy-2,2,6-trimethyl-3-(3-methylbut-2-enyl)cyclohexyl]methyl acetate (13.36%), β-sitosterol (9.27%), palmitic acid (8.44%), 3,7,11-trimethyl-1-dodecanol (7.76%), γ-sitosterol (6.86%), stigmasterol (4.79% and 3.65%) and campesterol (3.12% and 2.80%). Root extracts revealed l-(+)-ascorbic acid 2,6-dihexadecanoate (18.66%), dibutyl phthalate (15.42%), γ-sitosterol (12.54%), stearic acid (10.50%), 10-heneicosene (8.71%), β-amyrin (6.65%), stigmasterol (6.04%), E-15-heptadecenal (5.28%), n-tetracosanol-1 (5.08%) and campesterol (4.20%). In addition, the methanol and EA stem extracts reported l-(+)-ascorbic acid 2,6-dihexadecanoate (15.95% and 17.55%) followed by β-sitosterol (13.40%), methyl 8-oxo-17-octadecene-9,11-diynoate (7.51%), stigmasterol (6.71%), γ-sitosterol (6.35%), hexahydrofarnesyl acetone (5.77%) and campesterol (4.32%) as major compounds. GC-MS analysis of callus revealed 23 and 19 compounds in methnol and EA extracts, respectively. The major compounds detected were l-(+)-ascorbic acid, 2,6-dihexadecanoate (16.18% and 20.78%), palmitic acid ethyl ester (6.70% and 8.60%), eicosane (8.04%), hexahydrofarnesyl acetone (7.24%), palmitic acid methyl ester (5.14% and 6.61%) and phthalic acid, di(2-propylpentyl) ester (5.88%) (Godara et al., 2019). Mohanty et al. (2015) identified *p*-coumaric acid, rutin, and quercetin from the most active fraction of *L. reticulata*. Natarajan and Dhas (2014) identified 1-dodecene, 3-tetradecene,(Z)-, methyl-10-undecenoate, cyclopentaneundecanoicacid, methyl ester, urs-12-en-24-oic acid, 3-oxo-methyl ester(+)-, azulene,1,2,3,4,5,6,7,8,8á-octahydro-1,4-dimethyl-7-(1-methylethenyl)-,(1s-(1a,7a,8aa)-, phytol, isopropyl linoleate, quercetin, and lupeol from the ethanol extract (Figure 29.1).

29.3 PHARMACOLOGY

29.3.1 ANTIPYRETIC ACTIVITY

Sneha et al. (2016a) studied the antipyretic activity of *L. reticulata* aqueous extract in different animal models. The extract found safe up to 2,000 mg/kg and the activity was carried out using Baker's yeast (*S. cerevisiae*) induced pyrexia in Wistar albino rats. The rectal body temperature was measured by using a digital thermometer coated with glycerine. Baker's yeast (20%)

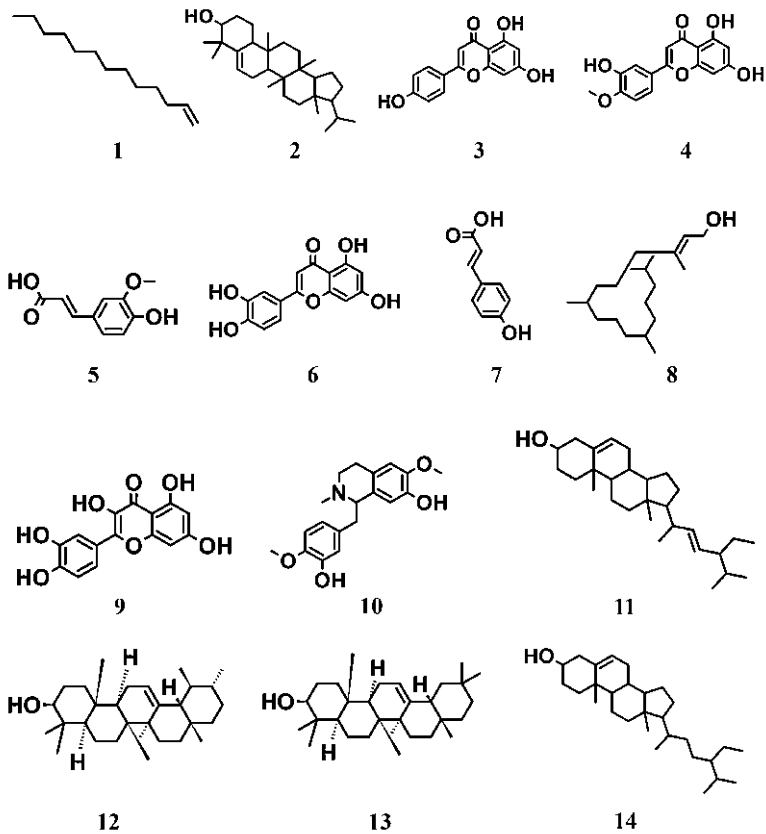


FIGURE 29.1 Structures of 1-tridecene (1); simiarenol (2); apigenin (3); diosmetin (4); ferulic acid (5); luteolin (6); *p*-coumaric acid (7); phytol (8); quercetin (9); reticulin (10); stigmasterol (11); alpha-amyrin (12); beta-amyrin (13); and β-sitosterol (14).

suspended in 0.9% saline was injected to the animals subcutaneously at 10 mL/kg b.w. dose. In Baker's yeast induced pyrexia in rats, the extract at 200 and 400 mg/kg dose significantly reduced the body temperature to 36.5 ± 0.1 and 35.8 ± 0.1°C, respectively after 22 hours of yeast administration, compared to the control group. Whereas, in case of cow milk induced pyrexia in rabbits, it reduced significantly the body temperature to 38.9 ± 0.09 and 38.6 ± 0.1°C after 6 hours of cow milk administration (at the doses 200 and 400 mg/kg dose, respectively) as compared to the control.

29.3.2 ANTI-INFLAMMATORY ACTIVITY

Sneha et al. (2016a) carried out anti-inflammatory activity of aqueous extract through carrageenan and turpentine oil induced paw edema in rat model. Group-I served as disease control and received 1% w/v carrageenan and saline; group-II (carrageenan 1% w/v) and 200 mg/kg b. w. AELR); group-III (1% w/v carrageenan and AELR 400 mg/kg b. w.) and group-IV (1% w/v carrageenan and 10 mg/kg b. w. indomethacin). The rats were administered orally with the respective drug one hour prior to the administration of carrageenan. Paw edema was measured hourly up to 4 hours by mercury plethysmometer to study the effect of aqueous extract on inflammation. In turpentine oil induced paw edema model, Group-I served as disease control (turpentine oil and saline); group-II (turpentine oil and 200 mg/kg b. w. AELR); group-III (turpentine oil and 400 mg/kg b. w. AELR) and group-IV (turpentine oil and 10 mg/kg b. w. indomethacin). Paw edema was measured up to 4 h. In both the models, the aqueous extract at 400 mg/kg dose showed 39.6 and 52.1% inhibitions, respectively.

Mohanty et al. (2015) investigated the anti-inflammatory activity of different extracts and fractions of *L. reticulata*. Significant increase in inhibition percentage of edema was noted in animals treated with EA fraction. The EA extract at 400 and 600 mg/kg doses reduced the edema by 40.25 and 60.59% respectively in carrageenan induced paw edema model. Whereas, in formalin induced paw edema, the EA fraction proved the higher efficiency in suppressing the edema with 39.91 and 59.24% inhibitions at 400 mg/kg dose. Diclofenac sodium showed notable inhibition (71.18 and 72.26%) in carrageenan and formalin induced edema models, respectively.

29.3.3 HEPATOPROTECTIVE ACTIVITY

Nema et al. (2011) evaluated the hepatoprotective activity of aqueous and ethanol extracts of stem in CCl_4 induced hepatotoxicity in rats. The toxicant CCl_4 used to induce the hepatotoxicity at 1.25 mL/kg dose with olive oil (1:1 composition). Ethanol and aqueous extracts were administered orally for seven days. The administration of CCl_4 to the animals revealed a marked increase in TB, SGOT, SGPT, and ALP. Oral administration of ethanol extract at 500 mg/kg revealed significant decrease in all the studied parameters [SGOT 85.45 ± 0.27 (U/L), SGPT 183.40 ± 0.12 (U/L), ALP 181.16 ± 0.11 (U/L) and TB 0.51 ± 0.10 (mg/dl) except total protein (8.90 ± 0.15 (g/dl)].

The extracts further normalized the depletion of total protein significantly when compared to CCl_4 treated group.

29.3.4 WOUND HEALING ACTIVITY

Sneha et al. (2016b) assessed the wound healing activity of aqueous extract using excision and burn wound models. In each model, animals were divided into three groups. Group I served as disease control group and received gel base, group II with 10% extract gel and group III as standard and received 10% ointment povidone-iodine. The extract gel in excision wound model showed a significant wound contraction (95.5 ± 0.2%) compared to the positive control povidone iodine (100 ± 0.0%) on 12th day. Period of epithelization in excision wound model was significantly reduced in the test sample (13.8 ± 0.40 days) as compared to disease control (26.5 ± 0.22). Similarly, results from burn wound model showed significant decrease in wound contraction (91.8 ± 0.2%) on 12th day and period of epithelization (15.1 ± 0.16 day) as compared to the positive control (100 ± 0.0% and 26.5 ± 0.22 days, respectively).

29.3.5 DIURETIC ACTIVITY

Mohanraj et al. (2012) evaluated the diuretic activity of whole plant extracts (aqueous and ethanol) in normal rats. Both the extracts were administered orally at 100 mg/kg dose. Furosemide (100 mg/kg) was used as control. Diuretic activity of the extracts was evaluated by measuring sodium, potassium, and chloride content, along with urine volume. Urine volume was significantly increased in both the extract treated groups (3.700 ± 0.07 and 3.200 ± 0.08 mL, respectively) compared to both negative and positive control groups (1.900 ± 0.04 and 4.100 ± 0.06 mL, respectively). Rats treated with 100 mg/kg aqueous extract revealed significant increase in Na^+, K^+ and Cl^- ions (14.13 ± 09, 85.12 ± 0.0, and 12.18 ± 0.8 meq/100 g, respectively) against the negative control group (11.22 ± 0.3, 72.00 ± 0.6, and 8.16 ± 0.58, meq/100 g, respectively).

29.3.6 ANTIOXIDANT ACTIVITY

Mohanty et al. (2014) evaluated the antioxidant potential of different solvent extracts of naturally grown and micro-propagated *L. reticulata* plants. The antioxidant potential was assessed by several antioxidant models *viz*. H_2O_2

scavenging, diphenylpicrylhydrazyl free radical scavenging and $FeCl_3$ reducing activities. The percent DPPH free radical scavenging activity from EA extract was noted to be the highest with the IC_{50} value of 267.13 µg/mL. Meanwhile, the methanolic extract showed moderate antioxidant activity with IC_{50} 510.15 µg/mL. The strong antioxidant potentiality of EA extract was also found against hydrogen peroxide (H_2O_2) and $FeCl_3$ radicals with the IC_{50} of 406.40 and 234.14 µg/mL, respectively.

Sonara and Saralaya (2012) evaluated polyphenol rich aerial part against scavenging of active oxygen species. The results indicated that the different extracts notably reduced the stable free radicals of DPPH with IC_{50} values 56.66, 55.55, and 47.20 µg/mL, respectively as compared to ascorbic acid (IC_{50} 40.70 µg/mL) and BHA (IC_{50} 61.74 µg/mL).

29.3.7 ANALGESIC ACTIVITY

Analgesic activity was tested using acetic acid induced writhing test in Wistar rats. The pretreatment with the test extract was followed by 1% acetic acid intraperitoneal injection (1000 µL/kg BW) to induce writhing. Further, writhing responses were counted after five minutes of acetic acid injection. Amongst all, the EA extract (400 and 600 µg/mL) exhibited a significant reduction in a number of writhing. Significant inhibition percentage of writhing was noted for EA extract (76.25 ± 2.85%) at 600 µg/mL compared to positive standard diclofenac sodium (85.72 ± 2.69%) (Mohanty et al., 2015).

29.3.8 ANTIMICROBIAL ACTIVITY

Kalidass et al. (2009) evaluated the antibacterial activity of ethanol, petroleum ether (PE) and chloroform extract of whole plant. The microorganisms used in the study included *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Streptococcus pyogenes, Salmonella typhi, Serratia marcescens, Klebsiella pneumoniae, Staphylococcus epidermidis, Proteus vulgaris,* and *Bacillus cereus.* Among the tested extracts, chloroform, and PE extracts showed the highest antimicrobial activity against *E. coli* and *K. pneumoniae,* respectively (zone of inhibition 22 mm each). Whereas, ethanol, and PE extracts revealed the highest antibacterial activity against *P. aeruginosa* and *K. pneumoniae* (12 and 22 mm, respectively).

29.3.9 CYTOTOXIC ACTIVITY

Sathiyanarayanan et al. (2007) evaluated the effect of leaf ethanol extract against Dalton's ascitic lymphoma (DAL) induced in Swiss mice. After two days of cell induction, the animals were treated with 200 mg/kg of extract for 8 days. The packed cell volume, cancer cell number, decrease in tumor weight and increase in life span were evaluated along with hematological parameters on 11th day. A significant decrease in the cancer cell number, tumor weight, normalized hematological parameters and increase in the life span were noted in the extract treated group. The cancer cell numbers were reduced to $0.94 \pm 0.10 \times 10^6$ in the extract treated mice. Intraperitoneal administration of the extract decreased the packed cell volume to 37.8%. Further, percentage increase in lifespan of the extract treated mice was increased by 26.6%. In addition, RBC count was raised to $4.62 \pm 0.22 \times 10^5$ μL^{-1}; whereas, WBC count was significantly decreased to $5.26 \pm 0.62 \times 10^3$ μl^{-1}.

Mohanty et al. (2014) evaluated anti-proliferative potential of different solvent extracts of naturally grown and micropropagated plants against L6 (rat skeletal muscle cell line), MCF-7 (human breast adenocarcinoma cell lines) and HT29 (colon adenocarcinoma cell line). It was observed that both the EA extract of naturally grown and tissue cultured plants exhibited higher cytotoxicity with lower IC_{50} values against MCF-7, HT-29, and L6 cell lines (21, 26, and 22 µg/mL and 20, 30, and 18 µg/mL, respectively). IC_{50} values for the methanol extract of both field grown (120 and 110 µg/mL) and tissue cultured plant (136 and 118 µg/mL) showed moderate cytotoxicity against HT-29 and L6 cell lines, respectively. Methanol extract at a higher concentration (480 µg/mL) was found to inhibit 50% cell proliferation against MCF-7 cell line. The aqueous extract of both the samples showed minimal cytotoxicity with higher IC_{50} values against MCF-7 (780 and 740 µg/mL), HT-29 (840 and 840 µg/mL) and L6 (960 and 850 µg/mL) cell lines.

29.3.10 ANXIOLYTIC ACTIVITY

Rajpurohit et al. (2016) investigated the anxiolytic activity of *L. reticulata* ethanolic extract using elevated plus maze, light-dark, hole-board, and social-interaction test models in Wistar albino rats. The extract at oral dose of 400 mg/kg per body weight significantly increased time spent (26.0 ± 0.9%) and number of entries in open arms (3.5 ± 0.42%) in rat elevated plus

maze test. The percentage of time spent in light and number of transitions in light-dark test were also increased significantly (111.5 ± 6.79 and 3.83 ± 0.30%, respectively).

29.3.11 IMMUNOMODULATORY ACTIVITY

Pravansha et al. (2012) tested the immunomodulatory effect of *L. reticulata* ethanolic leaf and root extracts in rodents at 100 and 200 mg/kg doses. DTH response in cyclophosphamide-induced immune-suppressed rats was higher (1.093 ± 0.0042 mm) from the roots extract when compared to normal control (1.017 ± 0.0020 mm). Phagocytic index was also noted higher (0.084 ± 0.013) over the normal control (0.022 ± 0.001). Effect of ethanolic leaves extract (100 mg/kg) using neutrophil adhesion test in normal rats was studied and found 68.11 ± 0.82% neutrophil adhesion as against normal control (37.12 ± 2.49%). In addition, significant reduction of oxidative stress and proper management of antioxidant system accounted its immunomodulatory activity.

KEYWORDS

- **analgesic activity**
- **anti-inflammatory activity**
- **Dalton's ascitic lymphoma**
- **hepatoprotective activity**
- **immunomodulatory effect**
- ***Leptadenia reticulata***
- **pharmacology**

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CHAPTER 30

Comprehensive Overview of the Phytochemistry and Pharmacological Studies of the Genus *Lobelia*

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30.1 INTRODUCTION

The genus *Lobelia* L. is the second largest genus of the family Campanulaceae with 415 sp. and the largest genus among the sub-family Lobelioideae Burnett (Lammers, 2011). Immense diversity has been recorded within the members of *Lobelia* with respect to their habit, growth, system of reproduction, structure, and color of flowers, pollination syndromes and floral specialization, types of fruits, seed morphology, and chromosome number (Lammers, 2011). A number of *Lobelia* species like *L. inflata*, *L. nicotianifolia*, *L. cardinalis*, *L. chinensis*, *L. laxiflora*, *L. trigona*, *L. siphilitica*, *L. sessilifolia*, *L. polyphylla*, *L. portoricensis*, *L. tupa*, *L. purpurascens*, and *L. pyramidalis* have been used in traditional medicine system for treating various diseases (Folquitto et al., 2019; Zheng et al., 2021). Considering its traditional importance, this genus is explored widely for its active principles that facilitated uncovering of numerous novel bioactive compounds. This review aims to provide information about the traditional uses, phytochemistry, and pharmacological research of *Lobelia* sp.

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30.2 TRADITIONAL USES OF *LOBELIA* SPECIES

Lobelia species have been extensively used worldwide in the traditional and/or folk medicines in the form of powder, infusion, decoction, tincture, and syrup to cure various diseases. In India *L. nicotianifolia* is used in Ayurveda to treat pain and snakebites; decoction of flowers is used to treat fever, asthma, and bronchitis; leaves are used in wound healing; and roots for eye diseases (Tamboli et al., 2012; Vigneshwaran et al., 2014), while the leaves and inflorescences of *L. pyramidalis* are used to cure sciatica, back pain, fever, bronchitis, and asthma (Joshi et al., 2011). In the Eastern North America *L. inflata* is used for the treatment of respiratory diseases such as asthma and bronchitis, in smoking cessation, as an emetic, hypnotic, and astringent (Felpin and Lebreton, 2004; Kursinszki et al., 2008), while *L. cardinalis* formulations are consumed to cure typhoid and fever, and used as an emetic (Brown et al., 2016). In Chinese traditional medicine *L. sessilifolia* has been used to cure snakebite, cough, cirrhosis ascites, abscess, and phlegm (Sun et al., 2012) and *L. chinensis* is used as an antidote for poisons; for the treatment of edema, jaundice, liver, stomach, and intestinal disorders; and shows antiviral, antimicrobial, and anti-inflammatory properties (Kuo et al., 2011; Mei-Wan et al., 2014; Li et al., 2016). In Chile *L. tupa* is used as an abortifacient, hallucinogen, respiratory stimulant, and for smoking cessation (Villegas et al., 2014).

30.3 PHYTOCHEMISTRY OF *LOBELIA* SPECIES

Phytochemical investigations of *Lobelia* sp. revealed the presence of alkaloids, flavonoids, terpenoids, polyacetylenes, coumarins, fatty acids, neolignans, and amides. It is now evident from the literature survey that 46% *Lobelia* sp. are mainly characterized by the presence of alkaloids, specifically the piperidine alkaloids (Figure 30.1(a)) which contribute for the prime pharmacological activities in *Lobelia* sp. More than 20 piperidine alkaloids have been reported from *L. inflata* (Felpin and Lebreton, 2004). Lobeline (Figure 30.1(b)) is one such piperidine alkaloid that has gained maximum attention due to its distinctive pharmacological properties. Table 30.1 reveals the information about 35 alkaloids which have been till date isolated from different *Lobelia* sp. Flavonoids have been identified from approximately 25% of *Lobelia* sp. (Folquitto et al., 2019) and enumerated in Table 30.2. About 13% of *Lobelia* sp. contain terpenoids (Folquitto et al., 2019) and 10 terpenoids isolated and identified from *L. davidii* and *L. sessilifolia* are listed in Table 30.3. Table 30.4 displays 4 polyacetylenes isolated from *L.*

chinensis, *L. inflata* and *L. siphilitica*. Three coumarins have been isolated from *L. chinensis* (Table 30.5). Amides, fatty acids and acids isolated from *L. chinensis* are shown in Table 30.6.

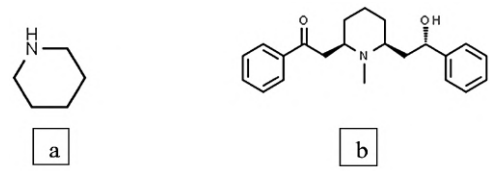


FIGURE 30.1 Chemical structure of (a) piperidine; and (b) lobeline alkaloid.

TABLE 30.1 Alkaloids isolated from *Lobelia* sp.

1.	Lobelanidine	Chloroform fraction of *L. nicotianifolia* (Gedeon and Gedeon, 1954); aerial parts of *L. tupa* (Kaczmarek and Steinegger, 1958); and *L. inflata* (Kursinszki et al., 2008).
2.	Lelobanidine	chloroform fraction of *L. nicotianifolia* (Gedeon and Gedeon, 1954).
3.	Lobelanine	Aerial parts of *L. tupa* (Kaczmarek and Steinegger, 1958) and *L. inflata* (Kursinszki et al., 2008).
4.	Lobeline	Aerial parts of *L. tupa* (Kaczmarek and Steinegger, 1958); *L. inflata* (Szoke et al., 1998); *L. urens* (Villegas et al., 2014); *L. portoricensis* (Melendez et al., 1967); *L. inflata* (Kursinszki et al., 2008); *L. nicotianifolia* (Tamboli et al., 2012); and *L. siphilitica* (Kesting et al., 2009).
5.	Norlobelanidine	Aerial parts of *L. tupa* and *L. inflata* (Villegas et al., 2014; Zhang et al., 1990; Weinges et al., 1972).
6.	Norlobelanine (=Portoricin)	Aerial parts of *L. tupa* (Kaczmarek and Steinegger, 1958); and *L. inflata* (Kursinszki et al., 2008).
7.	Lobinaline	Acid-base extraction of the $CHCl_3$ fraction of the methanolic extract of the aerial parts of *L. cardinalis* (Brown et al., 2016).
8.	8-phenylnorlobelol	Goldberg (1966)

9.	[N-methyl-2,6-bis(2-hydroxybutyl)-Δ3-piperidine]	Piperidine alkaloids isolated from total alkaloid extract of *L. berlandieri* (Williams et al., 1987); and *L. chinensis* (Yang et al., 2014).
10.	[N-methyl-2-(2-hydroxypropyl)-6-(2-hydroxybutyl)-Δ3-piperidine]	
11.	[N-methyl-2-(2-oxobutyl)-6-(2-hydroxybutyl-Δ3-piperidine]	
12.	Lelobanonoline	First identified in *L. davidii* (Zhang et al., 1990); and young stems of *L. polyphylla* (Villegas et al., 2014).
13.	cis-8,10-diethyl-1-3,4-dehydrolobelidiol	Leaves, stems, and flowers of *L. laxiflora* (Philipov et al., 1998; Rahman et al., 2014).
14.	Trans-8-ethyl-10-phenyl-3,4-dehydrolobelidiol	
15.	cis-8-ethyl-10-phenyl-3,4-dehydrolobelidiol	
16.	7-O-β-D-glucopyranosyl-α-homonojirimycin	Methanolic extract of *L. sessilifolia* (Ikeda et al., 2000).
17.	Radicamine A	Pyrrolidine alkaloids isolated from *L. chinensis* (Shibano et al., 2001).
18.	Radicamine B	
19.	Norlobeline	Aerial parts of *L. tupa* and *L. inflata* (Kursinszki et al., 2008).
20.	3-hydroxy-3-phenylpropanoic norallosedamine	
21.	3-hydroxy-3-phenylpropanoic allosedamine	
22.	8,10-dietillobelidione	Wang et al. (2008)
23.	(2R,6S,2″S)-2″-O-Acetyl lobeline	Crude extract of the aerial parts of *L. siphilitica* (Kesting et al., 2009).
24.	6-[E-2-(3-Methoxyphenyl) ethenyl]-2,3,4,5-tetrahydropyridine	
25.	8-propyl-10-phenyl lobelionol	Aerial parts of *L. tupa* and *L. inflata* (Kursinszki et al., 2008); and young stems of *L. polyphylla* (Villegas et al., 2014).
26.	1-(1-(2-hydroxy-2-phenylethyl)-1-methylpiperidin)butane-2-ol	Young stems of *L. polyphylla* (Villegas et al., 2014).
27.	1-(6-(2-hidroxypentyl)-1-methylpiperidin) butane-2-one	
28.	1-methyl-2-piperidinemethanol	
29.	Lobechine	Kuo et al. (2011)
30.	Lobechidine A	*L. chinensis* (Yang et al., 2014).
31.	Lobechidine B	
32.	Lobechidine C	
33.	Andrachcinidine A	
34.	Lophilacrin	Alkaloid fraction of *L. siphilitica* (Steinegger and Egger, 1952; Schmidt et al., 1957).
35.	Lophilin	

TABLE 30.2 Flavonoids isolated from *Lobelia* sp.

1.	Apigenin 7-O-rutinoside	Isolated and identified from *L. chinensis* (Zhou et al., 2008).
2.	Hesperidin	Isolated and identified from *L. chinensis* (Jiang et al., 2009; Wang et al., 2013).
3.	Apigenin	
4.	Rutin	Isolated and identified from *L. chinensis* (Wang et al., 2013).
5.	Hesperetin	
6.	Amentoflavone	
7.	Quercetin	
8.	Quercetin 3-O-α-L-rhaminoside	
9.	Quercetin 3-O-β-D-glucoside	
10.	Quercetin 7-O-α-L-rhaminoside	
11.	Chrysoeriol	
12.	Eupafolin	
13.	Narigenin	Isolated and identified from *L. chinensis* (Kuo et al., 2011; Wang et al., 2013).
14.	Luteolin	Isolated and identified from *L. chinensis* (Zhou et al., 2008; Jiang et al., 2009; Wang et al., 2013).
15.	Diosmetin	Isolated and identified from *L. chinensis* (Kuo et al., 2011; Jiang et al., 2009).
16.	Linarin	Isolated and identified from *L. chinensis* (Jiang et al., 2009; Zhou et al., 2008).
17.	Diosmin	
18.	Apigenin-7-O-[β-D-glucuronopyranosyl (1→2) O-β-glucuronopiranoside	Isolated and identified from *L. chinensis* (Kuo et al., 2011).
19.	Chrysoeriol-7-O-[β-D-glucuronopyranosyl (1→2) O-β-glucuronopiranoside	
20.	Delphinidin 3,5,3′-triglucoside	Anthocyanidins were identified in *L. erinus* (Yoshitama et al., 1977).
21.	Delphinidin 3-rutinoside-5,3′-glucoside	
22.	Lobelinin A	Anthocyanidins were identified in *L. erinus* (Kondo et al., 1989).
23.	Lobelinin B	

TABLE 30.3 Terpenoids isolated from *Lobelia* sp.

1.	Stigmasterol	Kuo et al. (2011)
2.	β-sitosterol	Isolated and identified from the hexane fraction of *L. davidii* (Zhang et al., 1990); isolated and identified from the aerial part of *L. sessilifolia* (Sun et al., 2012).
3.	β-amyrin	
4.	β-amyrin palmitate	
5.	Cycloeucalenol	
6.	Cycloeucalenol acetate	
7.	Daucosterol	Jiang et al. (2009)
8.	Oleanol 28-aldehyde 3-O-β-palmitate	Isolated and identified triterpenoid ester from the aerial part of *L. sessilifolia* (Sun et al., 2012).
9.	Ursolic acid	
10.	Oleanoic acid	

TABLE 30.4 Polyacetylenes isolated from *Lobelia* sp.

1.	Lobetyolin (9-O-β-D-glucopyranosyl-2,10-tetradecadien-4,6-diand-8,14-diol)	Reported from the *L. chinensis* (Yang et al., 2014); isolated from *L. inflata* hairy roots (Ishimaru et al., 1991; Balvanyos et al., 2004); isolated from the root extract of *L. siphilitica* (Kesting et al., 2009).
2.	Lobetyolinin	Reported from the *L. chinensis* (Yang et al., 2014).
3.	Isolobetyol	
4.	Lobetyol	Isolated from *L. inflata* hairy roots (Ishimaru et al., 1991); reported from the *L. chinensis* (Yang et al., 2014).

TABLE 30.5 Coumarins isolated from *Lobelia* sp.

1.	Scoparone	Isolated from *L. chinensis* (Kuo et al., 2011; Sun et al., 2012; Wang et al., 2013).
2.	Isoscopoletin	Isolated from *L. chinensis* (Wang et al., 2013).
3.	5,7-dymethoxy-8-hydroxycoumarin	Isolated from *L. chinensis* (Jiang et al., 2009; Sun et al., 2012).

TABLE 30.6 Amides, fatty acids, and acids isolated from *Lobelia* sp.

1.	Aurantiamide acetate	Isolated from *L. chinensis* (Kuo et al., 2011).
2.	Palmitic acid	Isolated and identified in *L. chinensis* (Jiang et al., 2009).
3.	Lacceroic acid	
4.	Stearic acid	

30.4 PHARMACOLOGICAL ACTIVITIES

30.4.1 ANTICONVULSANT ACTIVITY

Tamboli et al. (2012) investigated the anticonvulsant activity of lobeline isolated from leaf of *L. nicotianaefolia* in chemoconvulsant-induced seizures and the correlation was studied between the seizures and altered gamma amino butyric acid (GABA) in the brain of Swiss albino male mice in Pentylenetetrazol seizure models. Isolated lobeline at concentrations 10, 20, and 30 mg/kg significantly delayed and antagonized the onset of PTZ-induced and strychnine-induced seizures. A significant increase was observed in the brain GABA level at 20 mg/kg i.p. of isolated lobeline, thus postulating the pharmacological effects of lobeline which reduced the epileptic seizures via multiple mechanisms through GABAergic transmission. Anticonvulsant effect of *L. flaccida* leaf infusion extract was evaluated using pentylenetetrazole (PTZ)-induced convulsion model. Though the extract extended the latency and time of death caused by the PTZ, it did not significantly alter the onset of convulsion, exhibiting mild anticonvulsant activity (Stolom et al., 2016).

30.4.2 ANTI-INFLAMMATORY ACTIVITY

Anti-inflammatory property of ethanolic extracts of stems, leaves, and flowers, and three isolated alkaloids of *L. laxiflora* was assessed in two models of paw edema in mice namely, carrageenan (Car)- and cobra venom (CV)-induced *in vivo* models. The ethanolic extract of the flower significantly suppressed edema in both the models when compared with standard acetylsalicylic acid and indomethacin (Philipov et al., 1998). Forty six compounds were characterized from *L. chinensis*, of which particular isolates were screened for their inhibition of superoxide anion generation and elastase release. The crude methanolic *L. chinensis* extract exhibited 22.6% inhibition of superoxide anion generation, and 29.9% inhibition of elastase release in the FMLP/CB-activated human neutrophils at a concentration of 10 μg/mL (Kuo et al., 2011). Stolom et al. (2016) studied the anti-inflammatory activity of *L. flaccida* leaf infusion extract by the carrageenan-induced paw edema test in Wistar rats. The leaf infusion extract significantly inhibited paw edema induced by carrageenan, which was correlated with the presence of high flavonoids and/or saponins present in *L. flaccida*. Anti-inflammatory effect of *L. chinensis* was explored by Li et al. (2015). Initially quantification

of the polyphenol contents of methanolic extract of *L. chinensis* and fractions was performed, as polyphenols are well known to possess anti-inflammatory effects via scavenging ROS. High polyphenol content was recorded in the methanolic extract. The ethyl acetate (EA) fraction of *L. chinensis* (Lc-EA) showed better NO inhibition activity and the Lc-EA (62.5, 125, 250 mg/kg) pretreated rats showed a decline in the pro-inflammatory cytokines namely, TNF-α, IL-β, IL-6, and inhibited iNOS, COX-2 expression through the NF-κB pathway. Their outcomes suggested that *L. chinensis* revealed anti-inflammatory activity through the NF-κB pathways.

30.4.3 ANTIMICROBIAL ACTIVITY

Kuo et al. (2011) characterized 46 compounds from *L. chinensis*, of which selected isolates were screened for their inhibition of herpes simplex virus type-I (HSV-1) replication. The crude methanolic *L. chinensis* extract exhibited 19.8% inhibition against HSV-1 replication at a concentration of 100 μg/mL in the FMLP/CB-activated human neutrophils. Antimicrobial activity of essential oil from the aerial parts of *L. pyramidalis* was examined against gram positive bacteria (*Staphylococcus aureus*), gram negative bacteria (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli*) and fungi (*Candida albicans*, *Cryptococcus neoformans*, *Sporothrix schenckii*, *Trichophyton mentagrophytes*, *Aspergillus fumigatus* and *Candida parapsilosis*). The disc diffusion method indicated that all strains showed inhibition zones, except for *C. neoformans* and *K. pneumoniae*. The highest activity of essential oil was observed against bacterial strain *S. aureus* and fungal strain *T. mentagrophytes* with inhibition zones of 18 mm and 20 mm, respectively (Joshi et al., 2011). Nagananda et al. (2012) evaluated the antimicrobial activity of *L. inflata* which is widely used in traditional treatments for several respiratory disorders like asthma and bronchitis. They selected pathogens that were mainly associated with the respiratory tract, namely bacterial pathogens like *Klebsiella pneumoniae*, *Serratia marcescens* and *Staphylococcus aureus*, and fungal pathogens like *Aspergillus niger*, *Candida albicans* and *Cryptococcus neoformans*. The antimicrobial activities of aqueous, ethanolic, and methanolic extracts of leaf, root, stem, and inflorescence was evaluated. Highest antimicrobial activity was recorded for the methanolic inflorescence extract against *K. pneumoniae* and ethanolic inflorescence extract against *S. aureus*. Highest zone of inhibition was observed in the ethanolic extract of root and stem against *S. marcescens*. Aqueous extract of *L. inflata* did not exhibit antimicrobial activity against any studied pathogen. *In vitro*

antibacterial activity of *L. nicotianifolia* leaves extract using methanol, EA, acetone, chloroform, petroleum ether (PE) and water was studied against gram positive (*Staphylococcus aureus*) and gram negative (*Pseudomonas aeruginosa*, *Salmonella typhi*, and *Escherichia coli*) by agar well diffusion method. All the extracts inhibited the growth of the bacteria except PE and EA extracts. Methanolic leaf extract showed significant antibacterial activity against the bacterial pathogens as compared to the other extracts (Kalaimathi et al., 2015).

30.4.4 NEUROPROTECTIVE ACTIVITY

A high-throughput pharmacological screening (HTPS) was executed on numerous aqueous plant extracts to discover novel nicotinic acetylcholine receptor (nicAchR) ligands having superior therapeutic potential as neuroprotective agent. Nicotine activates nicAchRs present in the human central nervous system (CNS) and triggers its neuroprotective properties. *L. cardinalis* was identified as one of the plants with equipotent binding activity at $\alpha_4\beta_2$- and α_7-nicAchRs, and exhibited agonist activity on nicAchRs in SH-SY5Y cells, and inhibited [^{3}H]-dopamine (DA) uptake in rat striatal synaptosomes. Identification of lobinaline from *L. cardinalis* was the main source of the unique nicAchR binding profile. The *in vivo* electrochemical studies performed in the urethane-anesthetized male Sprague-Dawley rats demonstrated that when lobinaline was locally applied in the striatum, it significantly prolonged the clearance of exogenous DA by the dopamine transporter. They recommended lobinaline from *L. cardinalis* as a potential compound in the development of multi-functional neuroprotective agents in order to prevent DAergic neurotoxicity (Brown et al., 2016). The use of acetylcholinesterase (AChE) inhibitors is a promising treatment for the progressive degenerative neurologic disorder Alzheimer's disease. An investigation of total alkaloidal extracts of 31 Chinese herbal medicines was verified for their AChE inhibitory activities using the Ellman's technique and modified TLC bioautographic assay. Alkaloidal extract of *L. chinensis* exhibited 18.5% AChE inhibition at the final concentration of 100 µg/ml, indicating its potential in the treatment of Alzheimer's disease (Yang et al., 2012).

30.4.5 ANTI-TUMOR ACTIVITY

Effect of aqueous extract of *L. chinensis* was studied on precancerous colon lesions of Wistar rats induced by dimethylhydrazine (DMH) using the

aberrant crypt foci (ACF) model. The number of apoptotic cells in the colonic crypts of rats from the DMH group did not vary significantly as compared to the control group. A significant difference was observed between the group treated with *L. chinensis* and the control. The inhibition rate of low dose was 8.12%, medium dose was 59.42%, and high dose was 65.44%, which indicated that medium and high doses could significantly inhibit the ACF formation (Han et al., 2013). Liu et al. (2009) investigated the anti-cancer effects of *L. chinensis* on H22 hepatocellar carcinoma-bearing mice by adjusting P27 and surviving expression. The *L. chinensis* decoction exhibited stronger P27 and weaker surviving expression comparable to the positive control 5-fluorouracil. The *L. chinensis* decoction showed reduction in the H22 liver tumor size, achieving an anti-tumor rate of 33.98% which was remarkably lower as compared to the control group. A reduction in tumor weights in 39.48% of mice with significant difference compared to control indicated the potential of anticancer property of *L. chinensis* decoction. The anti-Hela cells effects of *L. chinensis* extracts were evaluated to study the influence of cardinal on cytoplasmatic free Ca^{2+} density. Co-incubation of 7.5 mg/mL extraction solution for 5 days led to the death of liver tumor cells by promoting intracellular Ca^{2+} release and extracellular Ca^{2+} withdrawal. Thus, increasing intra-cellular Ca^{2+} concentration could be the mechanism for promoting the tumor cell apoptosis (Gao et al., 2002). The development of drug resistance to anticancer compounds is mainly associated with the overexpression of ATP-binding cassette transporter proteins (Choi and Yu, 2014). Lobeline, in combination with doxorubicin, modulates the expression of P-glycoprotein (ABC transporters) to potentiate the chemotherapeutic effects of doxorubicin in breast cancer cell line (Ma and Wink, 2008). A recent study describes the cytotoxic potential of *L. nicotianifolia* crude extracts against breast cell lines (MCF-7 and MDA-MD-231) under *in vitro* conditions (Mankar et al., 2021).

30.4.6 INHIBITORY ACTIVITY AGAINST α-GLYCOSIDASES

Certain *Lobelia* species have validated potent inhibitory activity against α-glycosidases. Ikeda et al. (2000) isolated 7-O-β-D-glucopyranosyl-α-homonojirimycin from the 50% methanolic extract of *L. sessilifolia* whole plant, which showed potent inhibitory activity (IC_{50} = 0.1 μg/mL) against rice-α-glucosidase. Shibano et al. (2001) isolated two new pyrrolidine alkaloid, radicamine A and radicamine B from *L. chinensis*. These two

compounds, polyhydroxy alkaloids had an aromatic ring which could show interesting biological activities, similar to that of 1-de-oxynojirimycin.

30.4.7 IMMUNOMODULATING ACTIVITY

Plant polysaccharides show numerous bioactivities and possess the capacity to modulate immune function. The chemistry of polysaccharides purified from water extract of *L. chinensis* was analyzed and its immune modulating effect on the RAW 264.7 cell line was studied. A neutral α-glucan (BP1) having molecular mass of 9.45 kDa was isolated, which enhanced cell proliferation, phagocytosis, nitric oxide (NO) production, and cytokine secretion of RAW 264.7 cells in a dose-dependent manner (Li et al., 2016).

30.4.8 ANALGESIC ACTIVITY

Analgesic activity of water extract and 75% alcohol extract of *L. chinensis* was studied using mouse acetic acid-induced twisting test and hot plate test. The water extract significantly inhibited the twisting effect induced by acetic acid in the mice, and increased the threshold of pain in the mice after 1 h or 2 h treatment (Huang et al., 2012). Vigneshwaran et al. (2014) studied the analgesic activity of *L. nicotianifolia* leaves extract. Peripheral and central analgesic activity in mice was assessed chemically and thermally induced pain using acetic acid induced writhing model and Eddy's hotplate assay, respectively. The leaf extracts significantly inhibited the pain induced by Hotplate and acetic acid, indicating that it produced central and peripheral analgesic effect which was possibly due to the inhibition of chemical mediators and the presence of lobeline.

30.4.9 ANTIOXIDANT ACTIVITY

The antioxidant potential of *L. nicotianifolia* leaves and roots were studied by Kolap et al. (2021) using different solvents. Total phenolics, flavonoids, and lobeline content were analyzed. A correlation was observed in the total phenolics and flavonoids content of the leaf and root extracts with the studied antioxidant assays (ABTS, DPPH, hydroxyl radicals, NO, and H_2O_2). Their results indicated that the antioxidant activity was more attributed due to the phenolics and flavonoids in *L. nicotianifolia* plant parts.

30.4.10 ANTI-VENOM ACTIVITY

L. nicotianifolia has been traditionally used for treating snakebites. Vigneshwaran et al. (2014) studied the anti-venom activity of *L. nicotianifolia* leaf extracts using chloroform, ethanol, and water. Venom neutralizing ability of the three extracts was studied in Swiss albino mice against Russell's viper whole venom and its phospholipase 2 (PLA2) fractions. The LD_{50} and LD_{100} for whole Russell's viper venom were 8 μg/mice and 15 μg/mice, respectively. The LD_{50} and LD_{100} for the venom fraction rich in PLA2 activity was 12 μg/mice and 25 μg/mice, respectively. Ethanol fraction showed significant anti-venom activity as compared to chloroform and aqueous extracts.

30.4.11 RESPIRATORY STIMULATION IN ANIMALS

Meléndez et al. (1967) isolated a major alkaloid from the leaves of *L. portoricensis*, and the name suggested for the new alkaloid was portoricin (=norlobelanine). The action of lobeline and norlobelanine (=portoricin) was tested on the respiration and blood pressure in the dog. The alkaloids stimulated the respiratory center, with a marginal effect in the lowering of blood pressure. Similar results were studied in cats, Guinea pigs, and rabbits. It was found that lobeline and norlobelanine inhibited bronchospasms in the studied animals.

KEYWORDS

- **alkaloids**
- **gamma amino butyric acid**
- ***Lobelia chinensis***
- ***Lobelia nicotianifolia***
- **pentylenetetrazole**
- **respiratory stimulation**
- **terpenoids**

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CHAPTER 31

Bioactives and Pharmacology of *Matricaria chamomilla* L.

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31.1 INTRODUCTION

Matricaria chamomilla L., having a place with the family Asteraceae, is known as German chamomile. Chamomile is adopted as herbal remedies for an over kilo year. Chamomile has been part of southern and eastern Europe and widely grown in Germany, France, Russia, Brazil, and Yugoslavia. It was launched in India in the course of the Mughal period, now it is cultivated in Punjab, Uttar Pradesh, and Maharashtra, Jammu, and Kashmir (Das et

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al., 1998). It is an annual plant with erect stemmed branches and raises up to the tallness of 10 cm to 80 cm. *M. chamomile* is intermittently confused with plants of genera Anthems. Chamomile, a well-known Antiquity drug is known by a series of names as Babuna, Babunj, Roman chamomile, pin heads and scented may weed. Synonyms of this plant include *Matricaria recutita* L., *Chamomilla recutita* (L.) Rauschert., *Chamomilla vulgaris* Gray, etc.

Chamomile is largely used as an anti-inflammatory, antiseptic, and antispasmodic. The other pharmacological properties include carminative, healing, sedative, spasmolytic activity. Furthermore, to pharmaceutical uses, it is extensively cultivated in Europe and Asian countries for manufacturing its essential oil. The oil is lenient sedative being antibacterial (Mekonnen et al., 2016) and fungicidal in functioning. This aromatic oil is extensively utilized in perfumery, cosmetics (Leung et al., 1980), in aroma therapy and in food industry (Gosztola et al., 2010). The dry flowers of chamomile are in significant demand for its use in herbal tea (McKay et al., 2006) and for the treatment of hack and cold. Because of its considerable pharmacological and drug properties, the plant consequently possesses prominent economic value and it is in excess demand in European countries.

31.2 BIOACTIVES

Chamomile contains a large group of beneficially interesting and active compounds such as sesquiterpenes, flavonoids, coumarins, and polyacetylenes. The plant accommodates 0.24% to 1.9% volatile oil, when showed to steam refining, the oil goes in shading from splendid blue to dark green when new yet goes to dull yellow later stockpiling. The vital parts of the essential oil from the flowers are (E)-β-farnesene (4.9%–8.1%) (Satyal et al., 2015), terpene alcohol (farnesol), chamzulene (2.3%–10.9%) which is familiar for their anti-inflammatory, antiseptic, antiphlogistic, and spasmolytic properties. They are grouped into several major components α-bisabolol (Avonto et al., 2013) and chamazulene end up being more helpful than others. Beyond chamazulene, 120 chemical constituents have been recognized in chamomile flower as a secondary metabolite comprising of 28 terpenoids, 36 flavonoids, and 52 added compounds with promising pharmacological activity. Compounds, for example, α-bisabolol and cyclic ethers are antimicrobial, umbelliferone is fungistatic, while chamazulene and α-bisabolol are antiseptic in nature (Avonto et al., 2013). Bisabolol has been found to bring down how much proteolytic compound pepsin emitted by the stomach

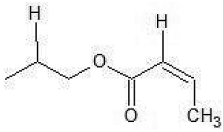
with practically no change happening in how much stomach acid, because of which it has been advanced for the treatment of gastric and upper gastrointestinal sicknesses. The presence of cis-en-yne-dicyclo ethers, perillyl liquor, triacontane, cadeleric hydrocarbon, and cadeleric tertiary liquor was accounted in chamomile. The main constituents of the blossoms additionally incorporate a few phenolic compounds, essentially the flavonoid apigenin, quercetin, patuletin, luteolin, and their glucosides (Figure 31.1).

31.3 PHARMACOLOGY

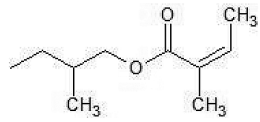
Chamomile (*Matricaria chamomilla*) is a notable therapeutic plant from the Asteraceae family frequently alluded to as the "star among restorative species." Nowadays, it is an exceptionally preferred and much utilized restorative plant in people and conventional medication. Its multitherapeutic, corrective, and dietary benefits have been set up through long periods of conventional and logical use and examination. Chamomile has a homegrown (Indian) and global market, which is expanding continuously. The plant accessible in the market multiple times is contaminated and subbed by direct relations of chamomile. Since chamomile is a rich wellspring of normal items, subtleties on compound constituents of natural balm and plant parts just as their pharmacological properties are incorporated. Besides, specific significance is given to the natural chemistry, biotechnology, market interest, and exchange of the plant. This review is an attempt to accumulate and document information on different aspects of chamomile and feature the requirement for innovative work (Singh et al., 2011).

31.3.1 ANTI-INFLAMMATORY ACTIVITY

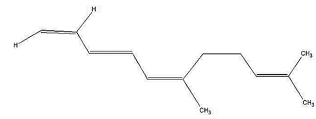
Compound identified with mitigating impact is apigenin, which is a flavonoid which is generally found in its glycosylated form, apegenin-7-glucoside (APG), in natural sources. But affectivity and protection of this glycoside have not been well explored for applying to the skin as medication. The anti-inflammatory calming action was affirmed by a decreased creation of TNF-α found in mice treated with APG followed by LPS treatment. In a clinical preliminary review, impacts of chamomile on foundational irritation were inspected. Mechanical joint capacity was improved and knee torment and furthermore lower back torment was diminished however no huge calming impacts were seen. In another clinical review, the viability of chamomile



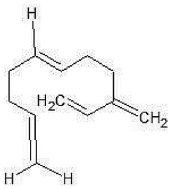
Isobutyl angelate



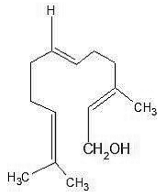
2-Methylbutyl angelate



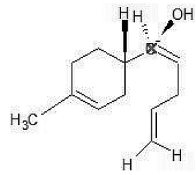
Farnesene



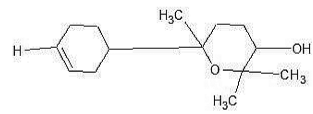
β-Farnesene



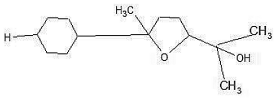
Farnesol



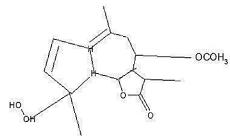
(-)-α-bisabolol



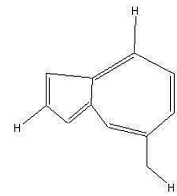
Bisabolol oxide A



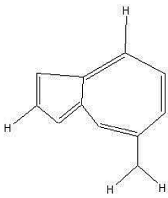
Bisabolol oxide B



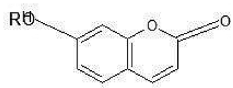
Matricin



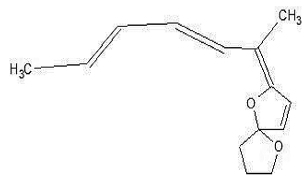
Chamazulene



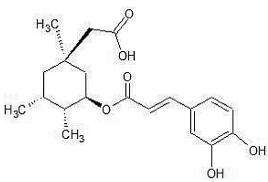
Guaiazulene



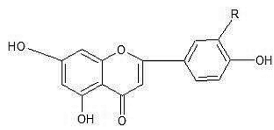
Umbelliferone



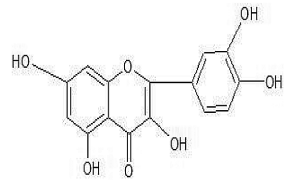
Z-Enyne dicloether



Chlorogenic acid



Luteolin



Quercetin

FIGURE 31.1 Production of secondary metabolites from *Matricaria chamomilla*.

separates as mouth flush was inspected and it showed that herbal mouth rinses were beneficial (Srivastava et al., 2009).

Shipochliev (1981) exhibited the plants positioned in the accompanying plunging request with respect to their strength raising impact on the uterus: chamomile (*Matricaria chamomilla* L.), potmarigold (*Calendula officinalis* L.), cockscomb (*Celosia cristata* L.), plantain (*Plantago lanceolata* L., *Plantago major* L., *Symphytum officinale* L.), shepherdspurse (*Capsella bursa-pastoris* L.), St. John's wort (*Hypericum perforatum* L.) in a last concentrate grouping of 1 to 2 mg unrefined medication for each 1 cm^3. The joined readiness 'Antiinflamin,' comprising of a pooled freeze-dried concentrate from three plants and chemotherapeutic specialists delivered a decent improving outcome, as 'comprets' for intrauterine application at the pace of one compret per 2,500 cm^3. Therefore, water extracts (mixtures) from a gathering of therapeutic plants were examined as far as their action upgrading the uterine strength in a progression of trials with a readiness of a separated bunny and guinea pig uterine horn.

Five plants such as *Myrtus communis, Apium graveolens, Matricaria chamomilla, Withania somnifera* and *Achilles santolina* from Iraq were evaluated for their calming action on flawless rodents by estimating the concealment of carrageenan-actuated paw edema delivered by l/10 of the intraperitoneal LD, dosages for the individual 80% ethanol extract. Acetylsalicylic acid was utilized as the standard medication. The plants showed the mitigating action with differing degrees and were characterized in the accompanying dropping request of action – *W. somnifera* > *A. graveolens* > *A. santolina* > *M. chamomilla* > *M. communis* (Al-Hindawi et al., 1989).

In an open multicentric review, 104 patients with gastrointestinal problems, for example, gastritis, tooting or minor fits of the stomach were dealt with orally for a long time with *Matricaria* bloom separate readiness (normalized to 50 mg of α-bisabolol and 150–300 mg apigenin 7-glucoside per 100 g) at an everyday portion of 5 mL. Hence, abstractly assessed side effects worked on in all patients and vanished in 44.2% of patients (Stiegelmeyer, 1978).

31.3.2 ANTIMICROBIAL ACTIVITY

Antimicrobial action of chamomile was surveyed, and it exposed that chamomile (–)-α-bisabolol synthase (MrBBS) incorporate enantiopure (–)-α-bisabolol as terpene and set off to create (–)-α-bisabolol (Moricz et al., 2013).

The antibacterial impact of the small amounts of chamomile was thought about in contrast to significant food-borne microbes – four gram-positive bacteria (*Campylobacter coli* – 0.40 mm, *Escherichia coli*, *Salmonella infantis* and *Bacillus cereus*) and two gram-negative bacteria (*Listeria monocytogenes* and *Staphylococcus aureus* – 0.35 mm). Consequences affirmed its antibacterial impact through its vitally medicinal balm parts, including coumarin, flavonoids, phenolic acids, and unsaturated fats (Mekinic et al., 2014). Antibacterial properties of chamomile extract were analyzed by green combination procedure; the outcomes showed that chamomile extricate (CE) comprised of nanometer structures. Furthermore, it was tracked down that AgNPs CE had multiple times higher antibacterial movement contrasted and CE AgNPs/G. In an *in vitro* and *in vivo* study, wound dressings movement of chamomile was assessed. Inhibitory zone with a breadth of around 7.6 mm was shaped (Parlinska-Wojtan et al., 2016).

Nougira et al. (2008) assessed the *in vitro* antimicrobial action of the accompanying plants: *Aleolanthus suaveolens, Caryophyllus aromaticus, Cymbopogon citratus, Matricaria chamomilla, Pithecellobium avaremotemo, Plectranthus amboinicus* and *Ruta graveolens* on the microbes that cause otitis externa. *Staphylococcus aureus* in 10 cultures, *Pseudomonas aeruginosa* in 8, *Pseudomonas aeruginosa* and *Staphylococcus aureus* together in 5 cultures and *Candida albicans* and *Candida krusei* in 4 cultures. *P. aeruginosa* was impervious to all oils and concentrates tried; extracts from *A. suaveolens, P. avaremotemo* and *R. graveolens* were dormant; the rejuvenating oil from *C. aromaticus* and *M. chamomila* were dynamic against 3 strains of *S. aureus* and the *Candida* strains; seven of the *S. aureus* strains were touchy to the *P. amboinicus* extract; notwithstanding, the oil was idle against 4 *S. aureus* strains and the *Candida strains* were touchy to the *R. graveolens* natural balm.

31.3.3 ANTIOXIDANT ACTIVITY

The level of bioactivity of watery concentrates of this plant was analyzed. Result showed that microencapsulated concentrates of this plant have higher cancer prevention agent action later the main week (Caleja et al., 2016). The cell reinforcement properties of chamomile, milk thorn, and halophilic microscopic organisms were researched. The outcome exhibited that various convergences of these normal parts had the option to restrain upregulation of H_2O_2-produced free extremists in human skin fibroblasts *in vitro* and subsequently have cancer prevention agent properties (Mamalis et al., 2013).

Cell reinforcement movement of blossom concentrate of chamomile was researched. Other than it was exhibited that CuO NPs has cell reinforcement action in a fixation subordinate way through breaking the DNA structure (Duman et al., 2016). Leaf and blossoms of feverfew, chamomile, and marigold were looked at in regards to their cancer prevention agent exercises, and it was observed that concentrates from bloom heads and leaves of chamomile are the most extravagant wellspring of cell reinforcement movement and among their synthetic mixtures; bisabolol and chamazulene have the most elevated cell reinforcements (Agatonovic-Kustrin et al., 2015). In an *in vitro* study, the harmfulness of chamomile was inspected. The discoveries exhibited the collection of Cr and huge plenitude in some mineral in roots just as abundance in oxidative pressure and release of glutathione (GSH) (Kovacik et al., 2014). In a creature study, the defensive impacts of concentrates of chamomile against receptive oxygen species were researched. The outcomes recommended that the concentrates abstain from creating reactive oxygen species and securing against hematological boundaries; changes in these properties might be because of its cell reinforcement properties, then again, came about because of its contrary impact on some intracellular middle people (Sebai et al., 2015). The concentrate of this plant can forestall the creation of synthetically dynamic species, and it might impede lipid peroxidation (LPO) through different cycles.

Cancer prevention agent properties of chamomile ethanol extract were inspected. Its cancer prevention agent property was affirmed by means of essence of high convergence of rosmarinic acid (Son et al., 2014). The design of filtered α-bisabolol was explained as (S, S)-α-bisabolol [or (–)-α-bisabolol]. In spite of the fact that *Matricaria recutita* α-bisabolol synthase (MrBBS) has a putative chloroplast-focusing on peptide, it was confined in the cytosol, and the cancellation of its N-terminal 23 amino acids essentially diminished its dependability and movement. Recombinant MrBBS showed motor properties similar to those of other sesquiterpene synthases. Accordingly, chamomile MrBBS combined enantiopure (–)-α-bisabolol as a solitary sesquiterpene item, opening a biotechnological freedom to deliver (–)-α-bisabolol.

31.3.4 ANTIDEPRESSIVE ACTIVITY

In a human report, the adequacy of chamomile tea on discouragement, sleep deprivation and weariness in ladies following labor was assessed and it was

shown that Chamomile tea might be utilized to decrease melancholy and further develop rest issues for post-pregnancy ladies (Chandra et al., 1973).

31.3.5 HEPATOPROTECTIVE ACTIVITY

The compound arrangement, cell reinforcement properties, and hepatoprotective impacts of sub-intense pre-therapy with chamomile decoction extract (CDE) against ethanol (EtOH)-actuated oxidative pressure in rodents was surveyed, and it was proposed that CDE applied a likely hepatoprotective impact against EtOH-initiated oxidative pressure in rodents, essentially partially, by adversely directing Fenton response parts, for example, H_2O_2 and free iron, which are known to prompt cytotoxicity interceded by intracellular calcium liberation (Sebai et al., 2015).

Hepatoprotective action of watery ethanolic concentrate of *Chamomile recutita* capitula against paracetamol incited hepatic harm in pale skinned person rodents was recognized by Gupta and Misra (2006). The impact of watery ethanolic concentrate of *Chamomile recutita* capitula on blood and liver GSH, Na+ K+-ATPase action, serum marker catalysts, serum bilirubin, glycogen, and thiobarbutiric acid responsive not really set in stone against paracetamol initiated harm in rodents. The concentrate of chamomile has inversion consequences for the degrees of previously mentioned boundaries in paracetamol hepatotoxicity. The concentrate of capitula of chamomile capacities as a hepatoprotective specialist. Thus, the hepatoprotective activity of chamomile might be due to the standardization of impeded layer work action (Gupta and Misra, 2006).

31.3.6 ANTI-DIABETIC ACTIVITY

Adequacy of blossom concentrates of chamomile for the treatment and anticipation of type 2 diabetes was explored. It showed a solid enemy of diabetic action through adjustment of PPARs and different elements (Weidner et al., 2013). The counter stoutness movement of chamomile tea was surveyed. Chamomile tea showed some helpful consequences for control of glucose and unsaturated fats in patients with type 2 diabetes (Rafraf et al., 2015). In a creature study on rodents, the counter hyperglycemic impacts of chamomile tea were explored, and it was shown that chamomile tea has a glucose-bringing down impact in diabetic rodents; along these lines, its everyday utilization can be possibly helpful in bringing down postprandial glucose levels (Khan et al., 2014).

Plants with antidiabetic exercises give significant sources to the improvement of new medications in the treatment of diabetes mellitus. Cemek et al. (2008) investigated the conceivable antihyperglycemic and antioxidative exercises of the ethereal piece of the *M. chamomilla* ethanolic extract (MCE) in streptozotocin (STZ; 70 mg/kg, i.p.)-actuated diabetic rodents. The accompanying gatherings were appointed; hoax (didn't get any substance), STZ + refined water (control), STZ + 5 mg/kg glibenclamide, STZ + 20 mg/kg MCE, STZ + 50 mg/kg MCE, STZ + 100 mg/kg MCE. Diabetic rodents were treated for 14 days by gavage. Postprandial blood glucose levels, malondialdehyde (MDA), diminished GSH, nitrate, nitrite, ascorbic acid, retinol, beta-carotene, superoxide dismutase, and catalase (CAT) levels were estimated, and immunohistochemical studies were acted in the gatherings as a whole. The acquired data uncovered that STZ brought about oxidative pressure and impacted the cancer prevention agent status. Treatment with various dosages of MCE fundamentally diminished postprandial hyperglycemia and oxidative pressure, and expanded the cell reinforcement framework. In histological examinations, MCE treatment ensured most of the pancreatic islet cells, as for the benchmark group. Thus, MCE showed huge antihyperglycemic impact and ensured b-cells in STZ-diabetic rodents, in a portion subordinate way, and decreased the hyperglycemia-related oxidative pressure (Cemek et al., 2008).

31.3.7 ANTIDIARRHEAL ACTIVITY

In a creature study, the defensive impacts of CE against the runs and oxidative pressure in rodents were researched. Results showed that concentrates of this plant have a solid antidiarrheal and cancer prevention agent properties in rodents in a portion subordinate way against castor oil-incited runs and digestive liquid collection (Sebai et al., 2014).

The clinical adequacy, security, and decency of an authorized natural blend of myrrh, espresso charcoal, and CEs in patients with manifestations of intense loose bowels was inspected, and it showed that the mix of myrrh, espresso charcoal, and chamomile blossom separate is powerful, all around endured, and alright for use in patients with side effects of intense the runs. The impacts are tantamount with customary treatments utilized in routine consideration (Albrecht et al., 2014). In this way, concentrates of the plant can play a critical part in keeping up with wellbeing and restoring illnesses on account of its unpredictable natural mixtures and its dynamic constituents, for example, terpenoids, flavonoids, quercetin, rutin, quercitrin, and gallic acid.

31.3.8 ANGIOGENESIS ACTIVITY

The antiangiogenic movement of CEs was assessed. Result showed that luteolin and apigenin have the most noteworthy limit in the advancement of fresh blood vessels and showed that these mixtures are engaged with the action uncovered by the methanolic extract (Guimaraes et al., 2016).

31.3.9 WOUND HEALING ACTIVITY

The wound healing actions were accomplished by mucous tissues development and not the presence of putrefaction and reposition of collagen filaments (Motealleh et al., 2014). Antibacterial and antifungal assessments showed an inhibitory zone with a width of around 7.6 mm. The rodent wound model outcomes likewise demonstrated that the examples stacked with 15% chamomile extract were astoundingly proficient to mend the injuries up to 99 ± 0.5% following 14 days post-treatment periods. The attachment of mesenchymal undeveloped cells and their suitability on the advanced examples were affirmed by MTT investigation. Likewise, the electrospun nanofibrous mats dependent on PCL/PS (65/35) showed a high productivity in the injury conclusion and recuperating process contrasted with the reference test, PCL/PS nanofibers without chamomile. Subsequently, the histology investigation uncovered that the arrangement of epithelial tissues, the absence of putrefaction and collagen filaments amassing in the dermis tissues for the above upgraded tests.

The examination of chamomile and corticosteroids for treating ulcers was done *in vitro* and *in vivo*. The trial bunches were control, *Chamomile recutita*, triamcinolone acetonide and clobetasol propionate. For the *in vitro*, concentrate on the cell suitability of fibroblasts refined for 24 h in media adapted by the substances was gotten by the MTT decrease examination. For the *in vivo* review, 125 male rodents were submitted to test ulcers treated or not (control) by the substances tried. At 1, 3, 5, 7, and after 14 days 5 creatures of each gathering were forfeited. The injuries were examined through clinical perception and histological injury recuperating reviewing. All test bunches introduced positive cell suitability in 24 h. The way of life treated with chamomile introduced the littlest cell reasonability. All creatures of the chamomile bunch displayed total injury mending 9 days before different gatherings. Complete fixed sores were seen following five days of treatment just in the chamomile bunch. Creatures treated with chamomile introduced essentially quicker twisted recuperating in contrast with those treated with

corticosteroids. In this way, the chamomile in contrast with corticosteroids advances quicker twisted recuperating process (Martins et al., 2009).

31.3.10 ANTILEISHMANIAL ACTIVITY

The chamazulene obtained from the *M. chamomilla* plant contribute to the therapeutic properties and was the most effective for the antileishmanial activity (Avonto et al., 2013).

31.3.11 IMMUNOMODULATION ACTIVITY

Uteshev et al. (1999) administered the heteropolysaccharides of *M. chamomilla* through intragastric and parenterally and found to normalize by developing insusceptible reaction upon air cooling and improve (but do not normalize) this processes upon immersion cooling. The immunomodulating effect of the heteropolysaccharides upon cooling was attributed to initiation of immunostimulant properties of heavy erythrocytes (macrocytes), activization of immunoregulation cells of peripheral blood, and increased sensitivity of effector cells to helper signals.

31.3.12 ANTI-ANXIETY ACTIVITY

Amsterdam et al. (2009) conducted an experiment on the controlled clinical preliminary of CE for generalized anxiety disorder (GAD). They likewise noticed an essentially more noteworthy decrease in mean all out Hamilton anxiety rating (HAM-A) score during chamomile versus fake treatment. Albeit the review was not controlled to recognize little to direct contrasts in auxiliary results, they noticed a positive change in all optional results in a similar way as the essential result measure. One patient in every treatment bunch suspended treatment for unfriendly occasions. The extent of patients encountering 0, 1, 2, or ≥3 adverse events was not significantly different between groups. Therefore, chamomile might have the humble anxiolytic movement in patients with gentle to direct GAD.

31.3.13 ANTI-BOTULISTIC ACTIVITY

Bianco et al. (2008) studied the commonness and spore-heap of *C. botulinum* in chamomile. They broke down 200 examples and the 7.5% of them were defiled with botulinum spores. Be that as it may, the pervasiveness of these

spores was essentially higher in chamomile sold by weight in home grown stores (opened up chamomile) than predominance in chamomile sold in tea sacks. The spore load identified in all certain examples was 0.3–0.4 spores per gram of chamomile. They recognized *C. botulinum* types A, B, and F in the 53.3%, 6.7%, and 13.3%, individually. Chamomile (chiefly, opened up chamomile) is an expected vehicle of *C. botulinum* spores, and ingestion of chamomile tea could address a danger for newborn child botulism. Hence, individuals use chamomile tea as a family solution for gastrointestinal colics and given this tea to newborn children.

31.3.14 ANTI-OSTEOPOROTIC ACTIVITY

Kassi et al. (2004) made an attempt to observe food parts possibly going about as selective estrogen receptor modulators (SERMs) with the four plant watery concentrates got from Greek vegetation (*Sideritis euboea, Sideritis clandestina, Marticaria chamomilla*, and *Pimpinella anisum*) in a progression of *in vitro* natural measures intelligent of SERM profile. They examined their capacity: (i) to invigorate the separation and mineralization of osteoblastic cell culture by histochemical staining for antacid phosphatase and Alizarin Red-S staining; (ii) to prompt, as antiestrogens, the insulin development factor restricting protein 3 (IGFBP3) in MCF-7 bosom malignant growth cells; and (iii) to multiply cervical adenocarcinoma (HeLa) cells by utilization of MTT measure. They uncovered that all the plant extracts learned at a fixation range 10–100 íg/mL invigorate osteoblastic cell separation and display antiestrogenic impact on bosom disease cells without proliferative consequences for cervical adenocarcinoma cells. The presence of estradiol repressed the antiestrogenic impact prompted by the concentrates on MCF-7 cells, proposing an estrogen receptor-related instrument. Therefore, the aqueous extracts derived from *S. euboea, S. clandestina, M. chamomilla,* and *P. anisum* may frame the premise to plan "useful food varieties" for the anticipation of osteoporosis.

31.3.15 ANTI-SEDATIVE ACTIVITY

Kesmati et al. (2008) showed that *Matricaria recutita* narcotic impact on agony, nervousness, and morphine withdrawal syndrome (MWS). The soothing properties of *M. recutita* in the presence and nonattendance of flumazenil as a benzodiazepine receptors bad guy in MWS were inspected utilizing the Wistar male grown-up rodents (250 ± 20 gr). Utilizing a vial

morphine sulfate arrangement, morphine reliance incited with expanding portions infusion subcutaneously at six days and on day seven the last portion was infused. Then, at that point, after four hours Naloxone (3 mg/kg, i.p.) was infused for acceptance of MWS. In each gathering, the withdrawal indications of climbing, bouncing, and face washing were estimated for 30 minutes quickly in presence and nonattendance of *M. recutita* extract (25 mg/kg) and Flumazenil (1 mg/kg). *M. recutita* diminished essentially the quantity of moving in contrast with control bunch, yet it had no critical impact on different signs. Flumazenil expanded essentially the indications of bouncing, face washing in contrast with control bunch. *M. recutita* within the sight of flumazenil had not calming impact and the climbing conduct expanded essentially. So, the sedative effect of *M. recutita* on morphine withdrawal syndrome was probably related to its benzodiazepine like parts that follow up on benzodiazepine receptors.

31.3.16 ANTI-ULCEROGENIC ACTIVITY

Extracts from the plants such as *Iberis amara, Melissa officinalis, Matricaria recutita, Carum carvi, Mentha x piperita, Glycyrrhiza glabra, Angelica archangelica, Silybum marianum*, and *Chelidonium majus*, separately, and joined as a business planning, STW 5 (Iberogast) and an altered detailing, STW 5-II, coming up short on the last three constituents, were tried for their potential enemy of ulcerogenic action against indomethacin incited gastric ulcers of the rodent just as for their antisecretory and cytoprotective exercises. All concentrates created a portion subordinate enemy of ulcerogenic movement related with a diminished acid result and an expanded mucin discharge, an increment in prostaglandin E2 discharge and a lessening in leukotrienes. The impact on pepsin content was somewhat factor and didn't appear to bear a relationship with the counter ulcerogenic movement. The most gainful impacts were seen with the consolidated details STW 5 and STW 5-II in a portion of 10 ml/kg b.w., tantamount with cimetidine in a portion of 100 mg/kg b.w. The counter ulcerogenic movement of the concentrates was additionally affirmed histologically. Thus, the cytoprotective consequence of the concentrates could be somewhat because of their flavonoid content and to their free extremist searching properties (Khayyal et al., 2001).

31.3.17 ANTI-PRURITIC ACTIVITY

The antipruritic impacts of the weight control plans containing German chamomile (*Matricaria recutita*) on the compound 48/80-initiated scratching

in ddY mice were analyzed by Kobayashi et al. (2003). Since it is accounted for that an infusion of compound 48/80, however, not histamine, actuated scratching conduct because of tingle but rather not to torment in ddY mice, compound 48/80-incited scratching in ddY mice is by all accounts a reasonable boundary for assessing antipruritic specialists autonomous of histamine receptor enmity. In the mice, taken care of the eating regimen containing 1.2 w/w% of the ethyl acetic acid derivation concentrate of dried bloom of German chamomile for 11 days, the compound 48/80-incited scratching conduct was fundamentally stifled. The ethyl acetic acid derivation concentrates of German chamomile portion conditionally smothered compound 48/80-initiated scratching without influencing body weight increment. The ethyl acetic acid derivation part of the ethanol separate and the ethanol concentrate of heated water extraction buildup of German chamomile bloom likewise showed the solid hindrance on the compound 48/80-prompted scratching. Thusly, inhibitory impacts of the dietary admission of the German CEs on compound 48/80-initiated tingle scratch reaction were practically identical to oxatomide (10 mg/kg, p.o.), an enemy of unfavorably susceptible specialist (Kobayashi et al., 2003).

The single peroral organization of the ethyl acetic acid derivation concentrate or rejuvenating oil of German chamomile showed momentous antipruritic impacts in the compound 48/80-initiated tingle scratching test in ddY mice. The ethyl acetic acid derivation concentrates or rejuvenating oil of German chamomile broke down in the vehicle of 10% ethanol, 10% Tween 80 and 80% physiological saline was orally administrated 2 h before pruritus incitement by compound 48/80 subcutaneous infusion. The ethyl acetic acid derivation concentrates or rejuvenating oil of German chamomile showed critical portion subordinate hindrance of the compound 48/80-prompted scratching without influencing unconstrained engine action. The antipruritic impacts of antihistamine H1 adversaries, oxatomide (10 mg/kg) and fexofenadine (10 mg/kg), were just incomplete in this test. Nonetheless, the antipruritic impacts of these specialists were strikingly improved by the joined organization of the ethyl acetic acid derivation concentrate of German chamomile (300 mg/kg). Along these lines, the co-prescription with the ethyl acetic acid derivation concentrate, or natural ointment of German chamomile and antihistamines may be compelling for the pruritus (Kobayashi et al., 2005).

31.3.18 ANTI-VIRAL ACTIVITY

Rejuvenating oils from anise, hyssop, thyme, ginger, chamomile, and sandalwood were evaluated for their inhibitory impact against the herpes simplex

virus type 2 (HSV-2) *in vitro* on RC-37 cells utilizing a plaque decrease measure by Koch et al. (2008). Genital herpes is an ongoing, constant contamination spreading productively and quietly as physically sent illness through the populace. Antiviral specialists right now applied for the treatment of herpesvirus contaminations incorporate acyclovir and its subsidiaries. The inhibitory fixations not set in stone at 0.016%, 0.0075%, 0.007%, 0.004%, 0.003% and 0.0015% for anise oil, hyssop oil, thyme oil, ginger oil, camomile oil and sandalwood oil, separately. An unmistakably portion subordinate virucidal action against HSV-2 could be exhibited for all natural ointments tried. Rejuvenating ointments were added at various stages during the viral contamination cycle to decide the method of the inhibitory impact. At greatest noncytotoxic convergences of the medicinal ointments, plaque arrangement was fundamentally diminished by over 90% when HSV-2 was preincubated with hyssop oil, thyme oil or ginger oil. Notwithstanding, no inhibitory impact could be seen when the medicinal ointments were added to the cells before disease with HSV-2 or later the adsorption period. Consequently, natural balms impacted HSV-2 basically before adsorption, presumably by collaborating with the viral envelope. Chamomile oil showed a high selectivity record and seems, by all accounts, to be a promising possibility for skin remedial application as virucidal specialists for treatment of herpes genitalis (Koch et al., 2008).

Vilaginès et al. (1985) made an attempt on the hydroalcoholic extract of *M. chamomilla* and the extract was added during the early stage of Poliovirus development that inhibits the cellular and viral RNA synthesis. Also, this inhibition was partially reversible.

31.3.19 LOUSICIDAL, OVICIDAL, AND REPELLENT ACTIVITY

The lousicidal and repellent impacts of five natural balms were inspected against the bison mite, *Haematopinus tuberculatus*, and flies swarming water bison in Qalyubia Governorate, Egypt. For the *in vitro* review, channel paper contact bioassays were utilized to test the oils and their deadly exercises were contrasted and that of d-phenothrin. Four minutes post-treatment, the middle deadly focus, LC_{50}, values were 2.74, 7.28, 12.35, 18.67, and 22.79% for camphor (*Cinnamomum camphora*), onion (*Allium cepa*), peppermint (*Mentha piperita*), chamomile (*Matricaria chamomilla*) and rosemary oils (*Rosmarinus officinalis*), separately, though for d-phenothrin, it was 1.17%. The deadly time (50) (LT_{50}) values were 0.89, 2.75, 15.39, 21.32, 11.60, and

1.94 min later treatment with 7.5% camphor, onion, peppermint, chamomile, rosemary, and dphenothrin, individually. Every one of the materials utilized, with the exception of rosemary, which was not applied, were ovicidal to the eggs of *H. tuberculatus*. Notwithstanding the aftereffects of the *in vitro* examines, the *in vivo* medicines uncovered that the pediculicidal action was more articulated with oils. All treated lice were killed later 0.5–2 min, while with d-phenothrin, 100% mortality was arrived at solely after 120 min. The quantity of lice pervading bison was fundamentally decreased 3, 6, 4, 6, and 9 days later treatment with camphor, peppermint, chamomile, onion, and d-phenothrin, individually. Besides, the oils and d-phenothrin fundamentally repulsed flies, *Musca domestica*, *Stomoxys calcitrans*, *Haematobia irritans* and *Hippobosca equina*, for 6 and 3 days post-treatment, individually. Thusly, some Egyptian medicinal oils showed potential for the improvement of new, fast, and safe lousicides and bug anti-agents for the controlling lice and flies which swarm water bison (Khater et al., 2009).

31.3.20 ANTICANCER ACTIVITY

Srivastava and Gupta (2007) assessed the anticancer properties of watery and methanolic extracts of chamomile against different human malignant growth cell lines. Openness of chamomile extracts caused negligible development inhibitory reactions in typical cells, though a critical abatement in cell suitability was seen in different human disease cell lines. Chamomile openness brought about differential apoptosis in malignant growth cells yet not in ordinary cells at comparable portions. HPLC examination of chamomile extract affirmed apigenin 7-O-glucoside as the significant constituent of chamomile; some minor glycoside parts were likewise noticed. Apigenin glucosides repressed disease cell development yet less significantly than the parent aglycone, apigenin. *Ex vivo* analyses recommended that deconjugation of glycosides happens *in vivo* to create aglycone, particularly in the small digestive tract. Therefore, the study addresses the showing of the anticancer impacts of chamomile.

31.3.21 CLEANING ACTIVITY

Sadr Lahijani et al. (2006) looked at the cleaning viability of chamomile hydroalcoholic concentrate and tea tree oil to 2.5% sodium hypochlorite (NaOCl) arrangement as an intracanal irrigant for the expulsion of the smear

layer. The best expulsion of smear layer happened with the utilization of NaOCl with a last flush of 17% EDTA (negative control) trailed by the utilization of a CE. CE was viewed as fundamentally more successful than refined water and tea tree oil. The utilization of a 2.5% NaOCl arrangement alone, without EDTA and that of tea tree oil, was found to have just minor impacts. Consequently, the adequacy of chamomile was better than NaOCl alone to eliminate smear layer yet not exactly NaOCl joined with EDTA.

31.3.22 HEMATOLOGICAL ACTIVITY

Pinto et al. (2008) assigned the social and hematological impacts of treatment with Chamomilla 6cH in mice exposed to trial stress. Swiss mice were arbitrarily partitioned into sets, one creature was vaccinated with Ehrlich's cancer, the different was dealt with day by day with Chamomilla 6cH or control or got no therapy. Following seven days, the creatures were seen in an open field and blood tests taken. Mice who cohabitated with a wiped out confine mate showed a diminishing in their overall movement, yet those treated with Chamomilla 6cH were less seriously impacted. In a subsequent examination, the constrained swimming test was applied to mice pre-treated with Chamomilla 6cH, controls were: water, 10% ethanol or amitriptyline. Just the amitriptyline and ethanol treated gatherings showed critical excitatory conduct, Chamomilla 6cH treated creatures' scores halfway between water control and ethanol or amitriptyline. A diminishing in the leukocyte include was seen in the amitriptyline and Chamomilla 6cH treated gatherings. Hence, the treatment with Chamomilla 6cH is identified with the recuperation of basal conduct conditions in mice exposed to distressing conditions.

31.3.23 ANTISOLAR ACTIVITY

Ramos et al. (1996) assessed the few plant extricates concerning bright retention spectra considering a potential application as antisolar specialists. Fluid and dry concentrates of *Hamamelis virginiana, Matricaria recutita, Aesculus hippocastanum, Rhamnus purshiana* and *Cinnamomum zeylanicum* were ready by repercolation, maceration, and microwave extraction. UVB retention spectra (290–320 nm) were obtained and the sun protection factors (SPF) of these arrangements were controlled by a spectrophotometric technique. Later fuse to a 2% arrangement of the manufactured sunscreen octylmethoxycinnamate, the concentrates showed a strengthening in SPF

esteems, recommending that this can be a fascinating technique to increase SPF. What's more, these concentrates can contribute their emollient and dampening properties to the item that shapes the significant qualities for ensuring skin against openness to the sun (Ramos et al., 1996).

31.3.24 ACARICIDAL ACTIVITY

Acaricidal properties decoctions, mixtures, and macerates of dried bloom heads of chamomile, *Matricaria chamomilla* were tried *in vitro* against the bug *Psoroptes cuniculi* Delafond (Parasitiformes: Psoroptidae). This parasite species is responsible for otoacariasis in homegrown creatures. Parasites were presented to the concentrates for 24, 48, or 72 h. Every one of the concentrates tried showed profoundly huge acaricidal movement when contrasted and controls. Among them, a decoction of 10% was the main detailing which gave 100% action at every one of the three perceptions times (Macchioni et al., 2004).

31.3.25 ANTI-GASTROINTESTINAL ACTIVITY

Mahady et al. (2005) distinguished and perceived the gram-negative bacterium *Helicobacter pylori* (HP), as the essential etiological variable related with the improvement of gastritis and peptic ulcer sickness. Moreover, HP contaminations are likewise connected with ongoing gastritis, gastric carcinoma and essential gastric B-cell lymphoma. Methanol concentrates of *Myristica fragrans* (seed) had a MIC of 12.5 μg/mL; *Zingiber officinale* (ginger rhizome/root) and *Rosmarinus officinalis* (rosemary leaf) had a MIC of 25 μg/mL. Methanol concentrates of botanicals with a MIC of 50 μg/mL included *Achillea millefolium*, *Foeniculum vulgare* (seed), *Passiflora incarnata* (spice), *Origanum majorana* (spice) and a (1:1) mix of *Curcuma longa* (root) and ginger rhizome. Natural concentrates with a MIC of 100 μg/mL included *Carum carvi* (seed), *Elettaria cardamomum* (seed), *Gentiana lutea* (roots), *Juniper communis* (berry), *Lavandula angustifolia* (blossoms), *Melissa officinalis* (leaves), *Mentha piperita* (leaves) and *Pimpinella anisum* (seed). Methanol concentrates of *Matricaria recutita* (blossoms) and *Ginkgo biloba* (leaves) had a MIC > 100 μg/mL. Consequently, numerous botanicals can be utilized as customary treatment for the gastrointestinal problems that restrain the *in vitro* development of HP, and have a preferred MIC than metronidazole. Since HP is the etiological agent responsible for dyspepsia,

gastritis, peptic ulcer disease, and gastric carcinoma, these data provide a plausible mechanism of action for these traditional medicines.

31.3.26 ANTI-GASTROINTESTINAL ACTIVITY

Mazokopakis et al. (2005) reported that methotrexate-induced oral mucositis in a patient with rheumatoid joint pain, effectively treated with Wild chamomile mouthwashes. Consequently, Oral mucositis is a known confusion of methotrexate treatment; however, a solitary solid mediation or specialist for prophylaxis.

KEYWORDS

- **anti-gastrointestinal activity**
- **apigenin-7-glucoside**
- **acaricidal properties**
- **chamomile extract**
- ***Chamomile recutita***
- **methotrexate**

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CHAPTER 32

Phytoconstituents and Pharmacological Potential of *Momordica cymbalaria* Fenzl. ex Naudin

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32.1 INTRODUCTION

Momordica cymbalaria Fenzl. ex Naudin is a perennial climber having thin, branched, and striated stem while the roots are woody. The other synonyms of the plant are *Luffa tuberosa* Roxb. and *Momordica tuberosa* Cogn. The outer view of leaves appear reniform with 5–7 lobes and deeply cordate at the base. The fruits are green, fleshy, long, ridged, and pyriform with curved peduncle at the base whereas the seeds are smooth, ovoid, shiny, and long. Flowers are unisexual, where the male flower has long peduncle, filiform, ebracteate with 2–5 flowers in a raceme possessing pale yellow corolla and bearing two stamens in each flower. However, the female flower is solitary with a longer peduncle. Propagation is through a few perennial tubers that survive in soil and reproduce in next season. The plant has been familiar in the Asian system of medicine since decades and the common names at various regions are Karchikai in Kannada, Athalakkai in Tamil or Kasarakayee in Telugu and has been known in the Asian traditional system of medicine since long time.

The fruits of *M. cymbalaria* are used as regular vegetable in South India, and the leaves are well consumed as leafy vegetable. Many of the regularly used vegetables are known to have health benefits which can be termed as neutraceuticals.

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32.2 BIOACTIVES

Momordica cymbalaria plant contains a wide variety of bioactive compounds like phenolic acids, flavonoids, carotenoids, proteins, triterpenoids, phytosterol, etc., with potential health benefits. The HPTLC fingerprinting in various solvents revealed the presence of secondary metabolites viz. flavonoids, steroids, phenols through macerated, refluxed, and soxhlated extracts which can be detected at 254 nm. The hypoglycemic ingredients of *M. cymbalaria* are phenolic acids, flavonoids, carotenoids, cucurbitane, triterpenoid, phytosterol, proteins, and glycosides.

A novel protein (M.W. 17 KDa) with isoelectric point (pI) 5.0 was identified as the active principle (antidiabetic) in the aqueous extract of the fruit, extracted through 20% ammonium sulfate fractionation followed by gel filtration chromatography and it was named as Mcy Protein. The N terminal amino acid sequence of Mcy protein was compared with the existing protein data bank. The N terminal amino acid sequences of the Mcy protein and A-chain of insulin are given below (Rajasekhar et al., 2010):

i. **Insulin α-Chain:** Gly Ile Val Glu Gln Cys Cys Thr Ser Leu Tyr-
ii. **Mcy Protein:** Gly Leu Glu Pro Thr Thr Thr-

The structural and functional characteristics of the Mcy protein are illustrated in Figure 32.1.

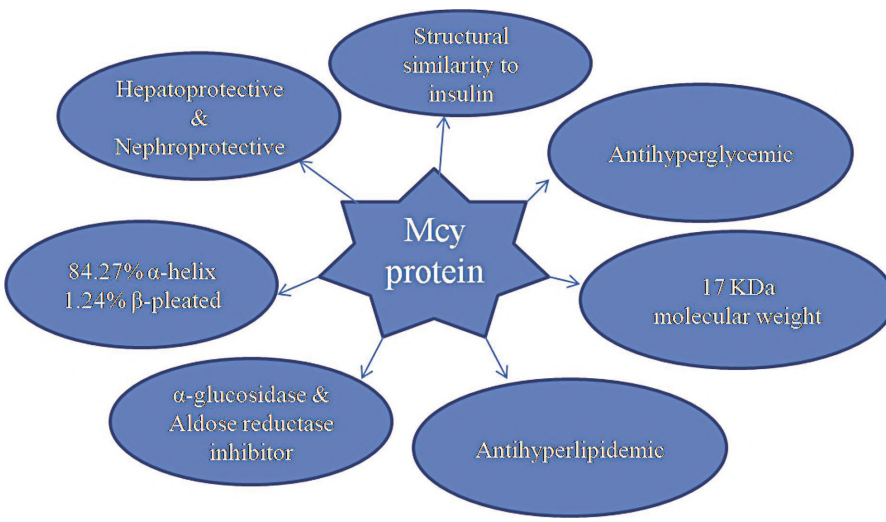


FIGURE 32.1 *Characteristics of Mcy protein.*

32.3 PHARMACOLOGY

The phytocomponents attribute to improvement in uptake of glucose and synthesis of glycogen in liver, muscle, and fat cells and the proteins exclusively augment release of insulin from pancreatic beta cells and/or regenerate insulin secreting beta cells (Jha et al., 2018). The phytoconstituents in *M. cymbalaria* exhibit a wide range of potential bioactivities like hepatoprotective (Swamy et al., 2008), cytotoxic (Dhasan and Jagadeesan, 2010), anti-inflammatory, cardiovascular (Koneri et al., 2015), antidiabetic (Rajasekhar et al., 2010) and antiparasitic effects. These actions are attributed by the tubers consisting of glycosides, β-sitosterol, steroidal saponin and starch, while the fruits and seeds compose numerous proteins, flavonoids, saponins, and conjugated fatty acids (punicic acid) and roots possessing other antioxidants.

M. cymbalaria herb belongs to such category owing to increased insulin secretion, enhanced uptake of glucose by adipose or muscle tissue besides inhibiting absorption of glucose from intestine and production of glucose from liver.

The Mcy protein had been proven to be novel with nearly 84% α-helix and 1% β-pleated sheet structure possessing significant antihyperglycemic effect @ 2.5 mg/kg body weight in STZ-induced diabetic rats (Rajasekhar et al., 2010). The investigation on the antihyperlipidemic and other biochemical activities of Mcy protein was done in comparison with glibenclamide as standard anti-diabetic drug in streptozotocin (STZ) induced diabetic rats treated for a period of 30 days (Saritha et al., 2015).

The wide pharmaceutical applications of *M. cymbalaria* in experimental animals and cell lines are presented in Table 32.1.

TABLE 32.1 Evidence-based pharmaceutical properties of *M. cymbalaria*

Phytocomponent	Nutraceutical/Pharmacological Properties	References
Lectin	Insulin like (linking together of 2 insulin receptors) bioactivity like lowering blood glucose concentrations, action on peripheral tissues and brain, suppressing appetite.	Mouhieddine et al. (1993)
Aqueous extract of fruit	Oral dosage of 0.5 g/kg b.w for 6 weeks showed significant antihyperglycemic and antihyperlipidemic effects as well in alloxan-induced diabetic rats.	Rao et al. (1999)
Aqueous fraction of fruit	Dosage of 0.5 g/kg b.w showed maximal blood glucose lowering effect in diabetic rats, but the same dosage did not produce any hypoglycemic activity in normal rats.	Rao et al. (2001)

TABLE 32.1 *(Continued)*

Phytocomponent	Nutraceutical/Pharmacological Properties	References
Aqueous extract of fruit	Aqueous extract of *Momordica cymbalaria* fruit (MC) (0.5 g/kg) treated through oral administration for 6 weeks showed significant antihyperglycemic as well as antihyperlipidemic effects in the alloxan-induced diabetic rats.	Kameswara Rao et al. (2003)
Ethanolic extract of roots	250 and 500 mg of ethanolic extract/kg b.w administered orally for 15 days significantly decreased the span of the estrous cycle and metaestrous phase increasing the prestrous phase. However, in both the treated groups, the diestrous phase was unaltered compared to the untreated. Both the doses demonstrated anti-ovulatory activity but the 500 mg/kg b.w. alone was proven to be abortifacient.	Koneri et al. (2006)
Fruit extract	Possess broad spectrum anti-microbial agents, also used in wound healing, intestinal disorders due to prominent inhibitory potential.	Swamy and Jayaveera (2005)
Saponin	Decrease in serum glucose level with marked increase in serum insulin and the glycogen level in the liver of diabetic rats.	Koneri et al. (2008)
Methanolic extract	Increase in tissue GSH level and decreased levels of lipid peroxides were noticed in paracetamol induced hepatitis in experimental rats on treatment with methanolic extract of *M. cymbalaria*. Elevated levels of biochemical markers like SGOT, SGPT, cholesterol, and bilirubin were also normalized.	Swamy et al. (2008)
Ethanolic extract	At a concentration of 500 mg/kg b.w *M. cymbalaria* prevented the alterations in marker enzymes of myocardial infarction and oxidative stress (Myocytosis including myofilamental alterations and degeneration of myofibrils) in rats with isoproterenol-induced myocardial injury.	Raju et al. (2008)
Saponins	Decreased blood glucose, cholesterol, triglycerides, and increased serum insulin, pancreatic islets, and β cells in diabetic BALB/C mice.	Firdous et al. (2009)
Aqueous extract	Anti-ulcer activity of the polyphenolic constituents was demonstrated by prominent reduction in non-protein sulfhydryls' concentration, gastric content, hemorrhage, and ulceration in ulcer induced albino Wistar rats.	Dhasan and Jagadeesan (2010)

TABLE 32.1 *(Continued)*

Phytocomponent	Nutraceutical/Pharmacological Properties	References
Methanol extract	Potent cytoprotective agent, effective in protecting gastric mucosa against aspirin-induced ulcers, inhibited pylorus ulcers, acid concentration and gastric volume and increased the pH values. The gastro protective function may probably be due to flavonoids.	Dhasan and Jagadeesan (2010)
Protein (Mcy)	Antidiabetic action was manifested by the presence of 17 KDa protein with a pI (isoelectric point) of 5.0. Intra peritoneal or i.v administration at 2.5 mg/kgb.w. significantly decreased the blood glucose levels from 300 mg/dl to 96.5 mg/dl besides HbA1c from 13 ± 0.72% to 7.6 ± 0.8% in streptozotocin induced diabetic albino Wistar rats.	Rajasekhar et al. (2010)
Methanolic extract	Oral administration in mice for 2 weeks at a dosage of 100 and 200 mg/kg significantly reduced the body weights, packed volume and viable tumor cell count compared to the mice in the EAC control group.	Jeevanantham et al. (2011)
Hydro-alcoholic extract of fruit	The anti-depressant action proved its efficacy as an adjuvant in the clinical treatment for neuro depression.	Vishal et al. (2011)
Ethanol and chloroform extracts	Minimum inhibitory concentration (MIC) with antifungal activity against the test organisms by microtiter plate assay ranged between 1 and 5 mg/ml. The extract at concentrations of 200 mM and 250 mM exhibited free radical scavenging activity of 49.8 and 42.3% respectively with Ascorbic acid as standard.	Balkhande and Surwase (2013)
Triterpenoid/ saponin in roots	Increased insulin secretion, modulation of Ca^{2+} channel and β cell rejuvenation (78%) in rat insulinoma cell line (RIF-5F).	Koneri et al. (2014)
Tuber's extract	Demonstrated nephroprotective effect by counteracting the toxicity induced by nephrotoxins, hence clinically effective in the treatment of acute renal injury.	Koneri et al. (2014)
Saponin rich methanolic extract	Peripheral neuroprotective effect has been improved in diabetic rats. Tail immersion latency time was decreased besides improving the pain sensitivity compared to untreated groups. Improvement in myelination and neuro degeneration effects was observed.	Koneri et al. (2014)
Saponin	*In vitro* anti-angiogenic and anticancer study in EAC revealed that inflammation in air pouch induced by carrageenan in rats and COX-2 derived PGE2 play a role in angiogenesis attributing to development of chronic granulation tissue.	Koneri et al. (2014)

TABLE 32.1 *(Continued)*

Phytocomponent	Nutraceutical/Pharmacological Properties	References
Methanolic extract of fruits	The outcome of the gene expression studies revealed the up-regulation of GLUT-4 and PPARγ in augmenting glucose uptake and also acting as PPARγ agonist in L6 myotubes.	Kumar et al. (2014)
Triterpenoid/ saponin of oleaonane type in roots	Increased uptake of glucose ~ 242.75% upon control in a study on L6 cell line.	Koneri et al. (2015)
Saponin	Demonstrated cardioprotective effect for ischemia induced myocardial damage in albino wistar rats and hypoxia ischemia induced cardiomyocyte cell death *in vitro*. Treatment with *M. cymbalaria* decreased the elevated levels *of* CK-MB and LDH in the heart tissue homogenate and improved the antioxidant defense system to overcome the stress induced by ischemia reperfusion.	Koneri et al. (2015)
HPLC purified steroidal saponin	*M. cymbalaria* significantly reverted the changes in tumor mean size and volume, progesterone, and luteinizing hormone, superoxide dismutase, catalase, glutathione, serum estradiol and follicle stimulating hormone in 50-day old female rats with DMBA (6 mg/kg) induced breast cancer. The chemopreventive effect is attributed to its antiestrogenic and antioxidant activity.	Kaskurthy et al. (2015)
Aqueous, ethanol, chloroform, and petroleum ether extracts	Plant extracts of aerial parts using water, ethanol, chloroform, and petroleum ether were screened for antimicrobial activity *in vitro* using agar diffusion method. The bacterial and fungal organisms used for testing are *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Aspergillus niger*, respectively. The extracts were proven to possess significant inhibitory activity against gram negative bacteria compared to standard antibiotics.	Sajjan et al. (2015)
Protein (Mcy)	Mcy protein also exhibited good therapeutic effects on hyperglycemia associated dyslipidemia. In serum and tissues the total cholesterol, HDL-cholesterol, LDL-cholesterol, and VLDL-cholesterol were normalized. Decrease in the elevated SGOT, SGPT, bilirubin, urea, and creatinine levels also prove the hepatic and renal protective effects.	Saritha et al. (2015)

TABLE 32.1 *(Continued)*

Phytocomponent	Nutraceutical/Pharmacological Properties	References
Protein (Mcy)	Circular dichroism spectroscopy revealed the structure of Mcy protein consisting of 84% α-helix and 1% β-pleated sheet.	Saritha et al. (2016)
Saponin	Improvement of muscular grip strength and velocity of nerve conduction was observed in the treated group. A significant decrease in the activities of sorbitol dehydrogenase (SDH) and aldose reductase (AR) was observed with lower sorbitol accumulation in the treated animals compared to the controls.	Samaddar et al. (2016a, b)
Saponin	Protective effect in NB-41A3 mouse neuroblastoma cells against high glucose (56 mM) induced neuropathy. The Na^+K^+-ATPase activity responsible for nerve conduction and appropriate membrane potential was restored on treatment with saponins, as evidenced by significant reduction in pro-inflammatory cytokine (IL-6, IL 1β, and TNF-α) production. These were increased considerably in high glucose-induced cells compared to normo glycemic (5.5 mM) state.	Samaddar et al. (2016a, b)
Steroidal saponins	Ameliorate humoral and cell-mediated immunity as well. Indirect hemagglutination test showed improved levels of serum immunoglobulins, circulating antibody titer and also exhibited a dose-related increase in the early hypersensitivity reaction to the SRBC (sheep red blood cells) antigen. Significantly improved the phagocytic index in carbon clearance assay, protection over cyclophosphamide-induced neutropenia and an increase in the adhesion of neutrophils was also noticed.	Rosey et al. (2016)
Butanol fraction	Macrophages, monocytes, and neutrophils' infiltration were reduced, where the action of endogenous factors were altered. The anti-inflammatory activity against carrageenan induced air-pouch model in wistar rats may probably be either by inhibition of the lysosomal enzymes or by stabilizing the membrane.	Reddy et al. (2018)
Hydroalcoholic extract	Elevated levels of serum albumin, total protein, urea, uric acid, and creatinine as an indication of kidney malfunction in sodium fluoride-induced nephrotoxicity in experimental animals were normalized. Oxidative stress parameters such as lipid peroxidation, glutathione, and catalase were improved on treatment with the extract at 200 and 400 mg/kg body weight for 30 days.	Rajesham et al. (2019)

KEYWORDS

- **antihyperglycemic**
- ***Aspergillus niger***
- ***Luffa tuberosa***
- **Mcy protein**
- **minimum inhibitory concentration**
- ***Momordica cymbalaria***
- **nephrotoxicity**
- **phytocomponents**

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CHAPTER 33

The Medicinal Properties of *Monteverdia ilicifolia* (Mart. ex Reissek) Biral

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33.1 INTRODUCTION

The *Monteverdia ilicifolia* (Mart. ex Reissek) Biral, formerly named *Maytenus ilicifolia* Mart. ex Reissek, is a small tree found in South America (Itokawa et al., 1994, CNCFlora, 2021). This species is registered in the Brazilian Pharmacopeia for alimentary and medicinal uses, especially the leaves, and because of its therapeutical properties, it was included in the National List of Essential Medicines in the Brazilian Unified Health System (RENISUS) (Hernandes et al., 2020). This tree can reach about 5 m high, with glabrous, tetra, or multifacial branches contained congested, leathery leaves and inflorescences in multiple flower fascicles (CNCFlora, 2021). In traditional medicine, this plant is used to treat inflammation, pain, stomach diseases and is a fertility-regulating and abortive agent (Itokawa et al., 1994; Beltrame et al., 2012, Hernandes et al., 2020, Brandelli et al., 2015).

33.2 BIOACTIVES

In the hexane and chloroform fractions of *M. ilicifolia* was identified high quantities of steroids, terpenoids, and flavonoids, especially the triterpene friedelin (Niero et al., 2001). In the ethyl acetate (EA) extract of the leaves,

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there were identified the terpenoids friedelin, friedelan-3-ol, α-tocopherol, T_1 and T_2 tocopherols, simiarenol, lupeol, lupenone, β-amyrin, β-sitosterol, stigmasterol, campesterol, ergosterol, brassicasterol, squalene, and hexadecanoic acid (Cordeiro et al., 1999). The abundant variety of terpenes were also observed in the leaves submitted to extraction with supercritical CO_2 (Mossi et al., 2010). The compounds are limonene, palmitic acid, geranyl acetate, phytol, squalene, vitamin E, stigmasterol, friedelan-3-ol, friedelina, and friedelan-3-one. In the methanolic extract was found the triterpenoids: betulin, betulin-3-caffeate, moradiol, erythrodiol, erythrodiol-3-caffeate, maytefolins (A, B, and C) and uvaol-3-caffeate (Ohsaki et al., 2004).

Leaves of this plant are also a rich source of flavonoids. In the hydromethanolic extract was identified rutin, hyperoside, isoquercitrin, and quercitrin (Tiberti et al., 2007). In the ethanol-soluble fraction was demonstrated the presence of the flavan-3-ols afzelechin, epiafzelechin, catechin, epicatechin, gallocatechin, and epigallocatechin (Souza et al., 2008a). The importance of this class of metabolites was showed by Beltrame and colleagues (2012), which identified the flavan-3-ol epicatechin and proposed that this compound could be used as a quality marker to herbal medicines containing *M. ilicifolia*.

Also, from the leaves of this plant was identified structural polysaccharides of the type I arabinogalactans, xylans, flavonol glycosides and type A proanthocyanins (Xavier and D'Angelo, 1996; Cipriani et al., 2004, 2008; Souza et al., 2008a, b). Glucosides identified as ilicifolinoside A, B, and C were obtained from the ethanolic extract of the leaves (Zhu et al., 1998). Other flavonoid glycosides were obtained from the aqueous infusion of the leaves namely kaempferol di-, tri-, and tetrasaccharides and quercetin trisaccharides (Leite et al., 2001).

Secondary metabolites with bioactive actions were also found in the roots of *M. ilicifolia*. In the methanolic extract was identified two new triterpenes named cangoronine and ilicifoline, respectively (Itokawa et al., 1991). In this same study, it was demonstrated the presence of maytenoic acid (polpunoic acid), D:B-friedoolean-5-en-3β,29-diol, D:A-friedoolean-29-ol-3-one, pristimerin, salasperimic acid, isopristimerin III and isotingenone III. Moreover, four triterpenes were isolated from the methanolic extract, with further revision of their structures, named as cangorosin A and B, isocangorosin A and 6,'7' dihydroisocangorosin A (Itokawa et al., 1990; Shirota et al., 1997). Four new triterpenes, named milicifolines (A-D), and the terpenoids tingenone, pristimerin, netzahuolcoyene, 7,8-dihydroxuxuarine Eα, 6-oxopristimerol, cheilocline C, β-sitosterol, and 7,8-dihydroscutidin αB were isolated from the *n*-hexane/Et_2O fraction of the root bark (Gutiérrez et al., 2007). In the

chloromethane-soluble fraction of a methanolic extract of the root bark, the sesquiterpene polyesters named cangorins A-J and the aromatic triterpene 6-oxotingenol were identified (Itokawa et al., 1993, 1994; Shirota et al., 1994).

The tissue culture of *M. ilicifolia* has been employed as a biotechnological tool to produce bioactive compounds, especially the quinone-methide triterpenoids (QMTs), which are chemotaxonomic markers of the family Celastraceae with various bioactive effects. It was demonstrated that the cell culture wielded the QMTs 22β-hidroxymaytenin and maytenin after chloroform extraction (Buffa-Filho et al., 2002). In the dichloromethane extract of the roots *in natura* and of callus and cell suspensions *in vitro* were detected the QMTs maytenin, 22β-hydroxymaytenin, celastrol, and pristimerin (Coppede et al., 2014).

In an ethnomedicine based study, Ahmed, and colleagues (1981) evaluated the content of ansmacrolides in decoctions of *M. ilicifolia* used by traditional folk to regulate fertility in women. It was found the presence of maytansine, maytanprine, and maytanbutine.

33.3 PHARMACOLOGY

33.3.1 GASTROPROTECTIVE EFFECTS

The aqueous extract of *M. ilicifolia* reduced acid secretion in gastric tissue isolated from frogs (Ferreira et al., 2004). The extract also inhibited acid secretion induced by histamine, indicating that it can interfere in histamine production and/or secretion. The gastroprotective role of this plant was also verified in ulcer lesions induced by cold-restraint stress in rats. The treatment with the aqueous, hexane, and ethyl-acetate extracts obtained from the leaves reduced ulcer lesions as also as the acid production in the gastric mucosa without causing toxicity (Jorge et al., 2004; Tabach et al., 2017a).

From the infusion of the leaves, Cipriani, and colleagues (2006) isolated a type I arabinogalactan that showed a protective effect on the gastric mucosa of rats exposed to 75% of ethanol. Also, from the leaves were obtained a type II arabinogalactan with similar gastroprotective effects (Baggio et al., 2012). Another structural polysaccharide of the xylan type and polygalacturonic acid isolated from *M. ilicifolia* leaves also prevented gastric lesions induced with ethanol in the rat (Cipriani et al., 2008, 2009).

The intraperitoneal treatment with the flavonoid-rich fraction obtained from the leaves protected against acute gastric lesions and promoted a

reduction in the chronic lesions in rats accompanied by the diminished secretion of gastric acid (Baggio et al., 2007). Moreover, the compound inhibited *in vitro* the activity of the H^+, K^+-ATPase. The flavonoid glycosides are likely to be responsible for these gastroprotective effects (Leite et al., 2010). Besides these effects, it was observed that the flavonoid-rich fraction from the leaves inhibited the gastrointestinal motility in mice, reducing gastric empty and intestinal transit after intraperitoneal administration in female mice (Baggio et al., 2009). This effect was related to a blockade in the muscarinic pathway. Similar results were observed for the aqueous extract, which delayed gastric emptying when administrated orally in rats, however, this effect was considered not clinically relevant (Siqueira et al., 2019).

An *in vitro* preliminary study showed that *M. ilicifolia* crude extract reduced the interleukin-8 (IL-8) secretion and the toll-like receptor 2 (*TLR2*) gene expression on human intestinal epithelial cell line Caco-2 after stimulation with lipoteichoic acid, without affecting the epithelial monolayer integrity, indicating a possible anti-inflammatory role on the intestinal mucosa (Wonfor et al., 2017).

Altogether, these studies corroborate with the traditional use of this plant in the treatment of dyspepsia, gastric ulcers, and intestinal disorders.

33.3.2 ANTINOCICEPTIVE AND ANTI-INFLAMMATORY EFFECTS

Despite the popular use in inflammatory disorders, there is little evidence in the literature regarding the role of *M. ilicifolia* in inflammatory processes. The hexane and ethylacetate extracts from the leaves inhibited nociception and formaldehyde-induced paw edema in mice and carrageenin-induced paw edema in rats (Jorge et al., 2004).

33.3.3 ANTINEOPLASTIC EFFECTS

The compound 6-oxotingenol isolated from the methanolic extract of the bark showed cytotoxicity against leukemia (L1210) and papilloma (KB) tumor cell lines (Shirota et al., 1994). The QMTs maytenin and its derivative compound 22-β-hydroxymaytenin isolated from cultured roots of the *M. ilicifolia* showed antiproliferative and antiapoptotic effects on squamous cell carcinoma lines *in vitro*. The compounds also augmented the production of reactive oxygen species (ROS) on these cells. Importantly, in a preliminary study, the maytenin administrated *in vivo* reduced cancer cell spreading in

SCID mice, similar to the standard drug cisplatin (Hernandes et al., 2020). Another QMT compound, the pristimerin, obtained from the leaves of the *M. ilicifolia* reduced the viability of leukemia (HL-60, K562), breast (MDA/MB-435), glioblastoma (SF-295) and colon (HCT-8) human cancer cells. Especially, this molecule inhibited DNA synthesis and induced cell death in the HL-60 cells (da Costa et al., 2008).

33.3.4 ANTIOXIDANT ACTIVITY

The crude *M. ilicifolia* roots ethanolic extract showed antioxidant effect when tested *in vitro* using the 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{\cdot+}$) assay and HOCl scavenger capacity assay (Vellosa et al., 2006). The hydroalcoholic extract of the leaves also has antioxidant properties, with higher efficiency when the leaves were dried at 40°C before the preparation of the extract (Negri et al., 2009). Also, the ethyl-acetate fraction of the crude acetone extract showed potent free radical scavenger capacity mainly because of the high content of condensed tannins such as procyanidins (Pessuto et al., 2009). A type II arabinogalactan isolated from the *M. ilicifolia* leaves showed *in vitro* antioxidant activity in the DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenger assay (Baggio et al., 2012).

33.3.5 ANTIVIRAL POTENTIAL

The aqueous and the hydroethanolic extracts of *M. ilicifolia* reduced *in vitro* the cytopathic effects (CPEs) of the herpes simplex virus type I on Vero cells (Montanha et al., 2004). Similarly, the ethanolic extract of the leaves showed inhibitory activity against the bovine herpesvirus type 5 (BHV-5) (Kohn et al., 2012).

33.3.6 ANTIMICROBIAL EFFECTS

Regarding the bactericide effects, the ethanolic extract from the leaves showed activity against the gram-positive bacteria *Staphylococcus aureus* (ATCC 25923) and the gram-negative bacteria *Klebsiella pneumoniae* (clinical isolate) with a minimum inhibition concentration (MIC) of 0.25 mg/mL (Ducat et al., 2011). Corroborating with these findings, the aqueous extract of the stems was capable of reducing growth and biofilm formation

of multi-drug resistant *K. pneumoniae,* carbapenemase (KPC)-producing bacterial clinical isolates of *K. pneumoniae, Enterobacter cloacae* and *Serratia marcescens* (Brandelli et al., 2015).

The methanolic extract of the *M. ilicifolia* leaves reduced *in vitro* the growth of *Cryptococcus neoformans* (ATCC 32608) (Braga et al., 2007). Pristimerin and maytenin obtained of *M. ilicifolia* showed potent antifungal activity against yeast and filamentous fungi such as *Candida albicans*, *Histoplasma capsulatum*, *Aspergillus niger* and *Trichophyton mentagrophytes*, with a high selectivity index (Gullo et al., 2012).

33.3.7 HYPOTENSIVE AND VASORELAXANT EFFECTS

The relaxant effect of this plant was demonstrated employing *in vitro* and *in vivo* studies. The extract and fractions obtained from the leaves provoked relaxation dependent on the endothelium in rat aorta rings related to nitric oxide (NO) production, guanylate cyclase and potassium channel activation (Rattmann et al., 2006). This *in vitro* effect was further observed *in vivo*, in which the intravenous injection of the extract and semi-purified fractions obtained from the leaves reduced the mean arterial pressure and heart rate of anesthetized rats in a NO/guanylate cyclase-dependent pathway (Crestani et al., 2009). Other *in vivo* evidence showed that a proanthocyanin-rich fraction of the leaves were able to induce diuresis and hypotensive action in rats, however, these effects were related to the activation of the prostaglandins/cyclic adenosine monophosphate (cAMP) pathway (Leme et al., 2013).

33.3.8 ANTIPROTOZOAL EFFECTS

The aqueous and ethanolic extract of *M. ilicifolia* the roots showed *in vitro* activity against *Leishmania amazonesis.* The ethanolic extract also had action against the *L. donovani* (Alvarenga et al., 2008). The quinonemethide triterpenes pristimerin and maytenin, and the alkaloids ilicifoliunines A and aquifoliunine E-I isolated from the *M. ilicifolia* root bark were effective against *Trypanosoma cruzi*, *L. amazonesis* and *L. chagasi* with low toxicity against murine macrophages (Santos et al., 2012, 2013).

33.3.9 TOXICITY

Pre-clinical studies did not indicate acute or chronic toxic effects under the administration of the *M. ilicifolia* (Ahmed et al., 1981; Oliveira et al., 1991;

Tabach et al., 2017a). Also, a high dose of the aqueous and ethanolic extracts of the leaves did not cause neurotoxicity in offspring nor alter the sperm quality of male rats (Ecker et al., 2017). A murine model demonstrated that the oral treatment with the hydroethanolic extract of the leaves in the pre-implantation period decreased the number of embryonic implantation sites and fetuses, but it did not cause embryotoxicity or morphological alteration in the female reproductive tract (Montanaria and Bevilacqua, 2002). In the same study, females treated with the extract had an augment in the uterus relative weight, indicating a potential estrogenic effect of this plant. Other findings showed that the hydroacetonic extract from the leaves is non-toxic to pregnant rats and did not affect the development of the offspring (Cunha-Laura et al., 2014).

In phase II clinical study, 24 healthy volunteers were subjected to the treatment with *M. ilicifolia* tablets in increasing weekly dosages, from 100 mg to 2,000 mg. No toxic or significant adverse effects were observed during the treatment, confirming the safety of this plant for human use (Tabach et al., 2017b).

KEYWORDS

- **antiprotozoal effects**
- **bovine herpesvirus**
- **hydroacetonic extract**
- **interleukin-8**
- ***Maytenus ilicifolia***
- ***Monteverdia ilicifolia***
- **quinone-methide triterpenoids**
- **reactive oxygen species**

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CHAPTER 34

Phytochemical Composition and Pharmacological Potential of *Myristica fragrans* Houtt.: A Review

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34.1 INTRODUCTION

Myristica fragrans Houtt. or nutmeg is an evergreen tropical plant having a pleasant aroma and taste. The plant belongs to the family Myristicaceae (Has, 2012; Olaleye et al., 2006). *M. fragrans* is widely grown in Banda Island in Moluccas of Indonesia, Penang Island of Malaysia, the West Indies, and the Kerala state of India (Somani et al., 2008).

M. fragrans (nutmeg) is a well-known aromatic perennial tree that grows about 5–13 m high, and occasionally up to 20 m. The bark contains watery pink or red sap. The leaves (5–15 × 2–7 cm) are alternately arranged along the branches, pointed, dark green-colored, the stems of which are approximately 1 cm long and the flowers are pale yellow, fleshy, waxy, bell-shaped, and usually single sexed, occasionally, both male and female flowers are found on the same tree (Gupta and Rajpurohit, 2011). The fruit is yellow in color, globose, with fleshy pericarp, and 6 to 9 cm long with a longitudinal ridge. The fruit of nutmeg is tropical spice and having pleasant aroma and strong taste, which is to enhance the taste of food, so nutmeg fruits are widely used as a flavoring agent in cakes, puddings, beverages, meat, sausages, etc. So the plants are widely cultivated in several countries, including Indonesia, Thailand, Japan, China, South Africa, and India (Arumugam et al., 2019).

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The fruit of *M. fragrans* has four parts – the skin, the fruit, the seed, and the mace. Fruit is a pendulous, succulent pericarp, the mace arillus covering the hard endocarp, and a wrinkled kernel with ruminated endosperm. When the arillus is fresh it has a brilliant scarlet color, when dry it is more of a horny, brittle texture, and a yellowish-brown color. The seed of nutmeg is firm, fleshy, whitish, traversed by reddish-brown veins, and contains plenty of oil. Skin, pulp, mace, and seed have been widely used in traditional Ayurvedic, Chinese, and Thai medicine (Somani et al., 2008).

In *M. fragrans*, three major commercial products are available such as mace, nutmeg, and essential oils (EOs) (Dorman et al., 1995). About 30–55% of the seed contain oils. Among these, there are two types of oils, including 5–15% of "volatile oil" and 24–40% fixed oil called "nutmeg butter" or expressed oil (Periasamy et al., 2016). The seeds are economically and medicinally important. The kernel obtained from the seeds is a popular condiment used as a spicing agent. The seeds are embedded in a white sweet-smelling pulp and are the most economically important part of the tree. They are also used as an aromatic stimulating additive to medicine and snuff. The nutmeg seed is one of the four components of the fruit obtained from the nutmeg tree (Prakash and Gupta, 2013).

34.2 PHYTOCHEMICAL COMPOSITION

Aromatic and medicinal plants have played key roles in the people by providing products for both food and medicine (Joshi et al., 2016). *M. fragrans* is a well-known aromatic plant with a characteristic pleasant aroma that possesses multiple medicinal applications. The plant is a source of high-value medicinal spices, and the nutmeg (endosperm) and mace (the reddish aril) having phytochemical activity (Latha et al., 2005). Several bioactive compounds were identified, including camphene, elemicin, eugenol, isoelemicin, isoeugenol, methoxyeugenol, pinene, sabinene, safrol, myristic acid, myristicin, elimicin, and lignan compounds (Capasso et al., 2000; Morita et al., 2003). Different studies were conducted on different parts of the plant, such as leaves (Zachariah et al., 2008), stem bark (Francis et al., 2019), and fruit pericarp (Francis et al., 2014) which revealed the presence of various phytochemicals such as lignans, neolignans, diphenylalkanes, phenylpropanoids, terpenoids, alkanes, fatty acids, fatty acid esters, and some of the minor constituents including steroids, saponins, triterpenoids, and flavonoids, etc. (Acuna et al., 2016).

The presence of aroma indicates the presence of volatile oil. The nutmeg contains volatile oils called myristicin which is an alkyl benzene derivative. The fixed oil contains myristic acid (Spricigo et al., 1999) trimiristicin (Mobarak et al., 1977), myristicanol A, Myristicanol B (Hattori et al., 1988), myrcene (Baldry et al., 1976). In addition to that, it also contains glycerides of fatty acids like oleic acid, palmitic acid (Harvey, 1975), tridecanoic acid, stearic acid, octanoic acid, pentadecanoic acid, macilenic acid, macilolic acid, acetic acid, gentisic acid, heptadecanoic acid, linoleic acid and meso-dihydro guaiaretic acid (Davis and Cooks, 1982). In the case of essential oil of nutmeg contains safrole, eugenol, alpha-terpineol, terpinolene, linalool, linalool acetate, limonene, 5-methoxy eugenol, dehydro-di-iso eugenol, iso eugenol, myristicin, elemicin, fragrasin, fragransol, paracoumaric acid, cineole (Ross, 2001), and these essential oil also possess sabinene, cymene, alpha-thujene, alpha-terpinene, and monoterpene alcohols (Ikeda et al., 1962). Along with fixed and volatile oils, it also contains some miscellaneous resorcinols like malabaricone B and malabaricone C (Jackson and Snowdon, 1990), licarin B, mace lignans, isolignans. Mace of nutmeg contains irregular amounts of amylodextrin, whereas, nutmeg seeds contain starch instead of amylodextrin. Amylodextrin is responsible for giving red color to mace with a solution of iodine (Hallström and Thuvander, 1997).

The 80% of the essential oil of nutmeg contains myristicin, elemicin, safrole, and sabinene (Maya et al., 2004). Mace oil have higher myristicin content than nutmeg seed oil (Sohn et al., 2007). The GC-MS analysis of nutmeg oil reveals that the presence of α-pinene, β-pinene, and sabinene constituted 77.38% and in mace oil, these compounds are present 60.76% (Gopalakrishnan, 1992). Some of the compounds are present in less concentration, such as limonene (4%), γ-terpinene (3.9%) in nutmeg oil and 6.6% in mace oil, terpinolene (3.3% in mace oil), terpinene-4-ol (7.2% in nutmeg oil and 23.6% in mace oil), methyl euginol (3.7% in mace oil) (Mallavarapu and Ramesh, 1998).

In *M. fragrans,* the essential oil contains a main psychoactive substance called myristicin (Ehrenpreis et al., 2014). Myristicin is chemically named 5-allyl-1-methoxy-2,3 or methylenedioxy benzene. This is the compound that gives aroma to the plant and produces significant psychopharmacological activity and insecticidal activity (Lee et al., 1998). Apart from natural sources, myristicin can be produced synthetically, because of its hallucinogenic effects. Hallucinogens are agents which are basically psychoactive substances that forcefully alter perception, mood, and a host of cognitive processes (Nichols, 2004). Since myristicin is a hallucinogen agent, it can be

used as a cheap hallucinogenic intoxicant; however, frequent usage can lead to fatal incidents resulting in organ damage and impact on the cardiovascular systems. Recently, many cases of nutmeg poisoning have been reported, including several fatal myristicin cases (Sangalli et al., 2000).

34.3 PHARMACOLOGICAL STUDIES

Medicinal plants have been used to relieve illness and maintain health for a long time. *M. fragrans* is a highly desired spice. In the 17th century, physicians claimed that nutmeg was used to cure many sicknesses (Flaumenhaft, 1982). During the 12th century, *M. fragrans* was imported into Europe by Arab merchants. It was used for many applications in folk medicine for the treatment of various diseases like antithrombotic, antitumor, and anti-inflammatory (Badet, 2011).

34.3.1 ANTIMICROBIAL ACTIVITIES

Apart from the folk medicinal activity, the aromatic herbs are also reported to have antioxidant and antimicrobial properties (Kelen and Tepe, 2008). Nutmeg has the ability to reduce symptoms associated with digestive problems, such as nausea and vomiting, and can increase appetite. According to the study of Gupta et al. (2013), the acetone extract of nutmeg possesses stronger antibacterial and antifungal activity against *Staphylococcus aureus* and *Aspergillus niger*, respectively. The report of Rani and Khullar (2004) showed that the methanolic extract of *M. fragrans* seeds have strong antibacterial activity against multi-drug resistant bacteria called *Salmonella typhi*. The ethyl acetate (EA) and ethanol extracts of *M. fragrans* was evaluated for the bactericidal potential against three Gram-positive cariogenic bacteria like *Streptococcus mutans* ATCC 25175, *Streptococcus mitis* ATCC 6249, and *Streptococcus salivarius* ATCC 13419 and three Gram-negative periodontopathic bacteria like *Aggregatibacter actinomycetemcomitans* ATCC 29522, *Porphyromonas gingivalis* ATCC 33277, and *Fusobacterium nucleatum* ATCC 25586 and showed a significant antibacterial activity (Narasimhan and Dhake, 2006). In addition to the extract, the oil of the plant also possesses potent antimicrobial activity against the tested human and plant pathogenic bacteria and fungi. The oil showed significant inhibitory activity against the bacteria, *Enterococcus faecalis*, *Lactococcus plantarum*, and *Proteus vulgaris* and the fungus *Candida tropicalis*, *Candida albicans*, *Rhizomucor*

miehei, and *Candida glabrata*. No inhibitory activity was observed against the bacteria *Clostridium perfringens*, *Klebsiella pneumoniae*, and *Bacillus megaterium*. There is no inhibitory activity of oil against the fungi, *Aspergillus niger* and *Aspergillus fumigatus* (Mary et al., 2012).

34.3.2 ANTIOXIDANT ACTIVITY

The antioxidant capacities of *M. fragrans* were investigated by various chemical assays, and several studies were reported to the efficiency of antioxidant activity of the plant. The essential oil and the extract obtained from the plant showed a potent antioxidant activity against various assay like total phenolic concentration, capacity to scavenge the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), inhibition of lipid peroxidation (LPO), inhibition of β-carotene bleaching, ability to chelate iron (II) ions, ferric reducing/antioxidant power assay (FRAP), etc. (Gupta et al., 2013; Kapoor et al., 2013; Zhang et al., 2015). Some of the studies reveals that the antioxidant property of the plant may be due to the presence of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) (Kapoor et al., 2013). The acetone extract of *M. fragrans* showed the presence of lignans which have the ability to scavenge 1,1′-diphenyl-2-picrylhydrazyl (DPPH) radical, inhibit LPO and protect plasmid DNA damage upon exposure to gamma radiation (Chatterjee et al., 2007). Another study on nutmeg oil revealed their potent antioxidant activity. The nutmeg oil effectively inhibited the oxidation of linoleic acid with 88.6% (Piaru et al., 2012). According to Zhang et al. (2015), the hexane, EA, and methanolic extracts of pericarps of *M. fragrans* contain neolignans and also showed good antioxidant activity in the LPO inhibitory antioxidant assay.

34.3.3 CYTOTOXIC, ANTICANCER, AND CHEMOPREVENTIVE ACTIVITIES

In addition to the antioxidant activity, the plant has a promising anticancer activity. Several reports are to be shown that the plant has potent anticancer activity. The ethanolic extract of seed of *M. fragrans* showed promising anticancer activity against seven human cancer cell lines and reveals that the ethanolic extract of nutmeg possess possible cytotoxic and anticancer properties against several cells by SRB method (Prakash and Gupta, 2013).

The ethanolic extract of nutmeg strongly suppressed the growth of human lymphoid, leukemia Molt 4 B cells (Moteki et al., 2002).

In addition to the extract, oil also has potent anticancer activity. Various concentrations of essential oil in the MCF-7 breast cancer cell line and A-357 epidermal skin cancer cell line showed an efficient cytotoxic activity (Mary et al., 2012). Myristicin was considered a potential chemopreventive agent because it induces a detoxifying enzyme called glutathione (GSH) S-transferase in the liver and small intestinal mucosa of mice to prevent cancer-inducing molecules (Zheng et al., 1992). The methanolic extract of *M. fragrans* acts as a potent anticancer agent in the Jurkat leukemic T-cell line (Borra et al., 2005).

34.3.4 HEPATOPROTECTIVE EFFECTS

Usually, spices possess hepatoprotective activity. Nutmeg has long been a highly desired spice and showed the most potent hepatoprotective activity in comparison with 21 other spices examined when orally administered to rats with liver damage caused by lipopolysaccharide (LPS) and D-galactosamine (D-GalN) and also found that myristicin, is the major compound in the essential oils (EOs) of nutmeg, and have extraordinarily potent hepatoprotective activity (Morita et al., 2003). The aqueous extract of *M. fragrans* seeds inhibited isoproterenol-induced hepatotoxicity, and from the study, it is clear that there are no more clinical complications as shown by oral toxicity studies using this plant (Kareem et al., 2013). Sohn et al. (2008) observed that the macelignan from *M. fragrans* have hepatoprotective effects.

34.3.5 ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES

The aril of the fruit of the plant possesses potent anti-inflammatory activity. The methanolic extract obtained from mace showed a lasting anti-inflammatory activity against carrageenin-induced edema in rats and acetic acid-induced vascular permeability in mice, and also from their studies, they found out that myristicin as a major factor responsible for anti-inflammatory action (Ozaki et al., 1989).

The report of Olajide et al. (2000) about the pharmacological properties of nutmeg oil was similar to those of non-steroidal anti-inflammatory drugs and also the oil possesses the analgesic effect in the acetic acid-induced writhing model, and in the late phase of the formalin-induced licking. The

chloroform extract of seeds demonstrated anti-inflammatory activity by inhibiting carrageenan-induced rat paw edema, as well as exhibiting a strong analgesic effect (Olajide et al., 1999).

34.3.6 CARDIOPROTECTIVE EFFECT

In ancient times, it was reported that nutmeg possesses cardio tonic properties and prevents oxidative stress. The seeds of *M. fragrans* administered to hypercholesterolemic rabbits showed a significant reduction in the low-density lipoproteins and serum cholesterol (Gupta, 2020). The aqueous extract of *M. fragrans* seeds has cardioprotective effect against myocardial infarction (MI). The pretreatment with the aqueous *M. fragrans* extract offered protection against isoproterenol effects on blood glucose, plasma lipids, as well as histological myocardial changes, suggesting a potential cardiovascular protective role of *M. fragrans* seed consumption (Kareem, 2009).

34.3.7 MISCELLANEOUS PHARMACOLOGICAL EFFECTS

Furthermore, nutmeg is said to have a variety of benefits, including antidiarrheal activity, antidiabetic, stimulant, antifungal, carminative, anti-inflammatory properties and neuroprotective activities (Asgarpanah and Kazemivash, 2012).

The effects of *M. fragrans* in the central nervous system (CNS) using the hexane extract elicited that it acts as a significant antidepressant-like effect in mice in the forced swim and tail suspension tests (Dhingra and Sharma, 2006).

Since the bark of *M. fragrans* methanol extract at 20 µg/ml extract induced apoptosis of Jurkat cells, and the extracts acts upon the SIRT1 gene expression as the minimum amount that could induce apoptosis (Sa-Nguanmoo and Poovorawan, 2007).

Some of the investigations reveal that the presence of certain compounds present in the plant may cause toxic effects. The two main phenylpropanoid constituents, such as myristicin and elemicin in *M. fragrans* seeds has been believed to be the main compounds for its toxic effects (Sonavane et al., 2002).

The seeds of the plant also possess hallucinogenic effects due to the presence of myristicin. Since myristicin is a hallucinogenic agent, it can be used

as a cheap hallucinogenic intoxicant; however, frequent usage can lead to fatal incidents resulting in organ damage and impact on the cardiovascular systems. Recently, many cases of nutmeg poisoning have been reported, including several fatal myristicin cases (Sangalli et al., 2000) and also myristicin has been known to produce significant psychopharmacological responses as well as insecticidal activity (Lee et al., 1998).

34.4 CONCLUSION

Nutmeg is a valuable cooking spice that has been used all over the world. Besides flavoring foods and beverages, nutmeg has also been used in traditional remedies for stomach and kidney disorders and possesses various pharmacological activities like antioxidant, antimicrobial, anti-inflammatory, hepatoprotective, etc. *M. fragrans*is a rich source of fixed and essential oil, triterpenes, and various types of phenolic compounds. Different secondary metabolites present in the nutmeg exhibit several pharmacological activities.

KEYWORDS

- **butylated hydroxytoluene**
- **hallucinogenic effects**
- **myocardial infarction**
- ***Myristica fragrans***
- **myristicin**
- **nutmeg**
- **spice**

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CHAPTER 35

Bioactivity Potential and Pharmacological Efficiency of *Piper betle* L.

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35.1 INTRODUCTION

Piper betle L. or Betel is a vine that belongs to the family Piperaceae widely used in Asia as Paan or betel quid and traditionally offered as a mark of respect or used in auspicious ceremonies. It is an important horticultural crop, considered recreational and used in several medicinal systems, especially in Asia (Khan et al., 2012). *P. betle* has over hundreds of varieties distributed in India, Bangladesh, the Philippine Islands, Myanmar, the Malay Peninsula, Malaysia, and Sri Lanka (Guha, 2006; Kumar et al., 2010), and Malaysia is considered as its origin place (Chattopadhyay and Maity, 1967). India has around 40 varieties of *P. betle* found in West Bengal, Orissa, Maharashtra, Uttar Pradesh, Tamil Nadu, and Madhya Pradesh (Madhumita et al., 2019). Commonly *P. betle* is known as Paan in Assamese/Urdu/Hindi/Odia/Bengali, and Tambula and Nagavalli in Sanskrit, Vetrilai in Tamil, Tamalapaku in Telugu, Vidyache pan in Marathi, Veeleyada yele in Kannada and Vettila in Malayalam. *P. betle* is a dioecious perennial creeper with deep green heart-shaped leaves and glabrous stems which produces adventitious roots at the

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nodes. The ovate or rounded leaves which are 8–18 cm. long and 6–10 cm. wide, narrowly, and sharply acuminate at the apex, cordate or subcordate and mostly asymmetric at the base, petiole 2–4 cm. long. Male and female flowers originated in spikes separately in different plants, axillary in position bearing numerous sessile florets that are bracteate, naked, and compactly arranged on the inflorescence axis. The matured male florets are yellow, with the two black stamens and other floret parts that modified into a bract embedded in the rachis. Stigmatic lobes are white, sessile, and present in mature female spikes. The number of stigmatic lobes in cultivars varied from six to nine. *P. betle* used in several traditional medicinal systems. In Ayurveda, it is used independently or along with different medic, in ancient text like Sushruta Samhita and Bhavaprakash Nighantu leaves of *P. betle* described as aromatic, sharp, hot, acrid, and beneficial for voice, laxative, appetizer, besides this, they pacify Vata and aggravate Pitta (Pradhan et al., 2013). *P. betle* leaves are used as mouth fresheners can treat several diseases such as bad breath, boils, and abscesses, conjunctivitis, constipation, swelling of gums, cuts, and injuries, cold, cough, bronchial asthma, rheumatism, stomachalgia, etc. The leaves also bear the essential oil which has antibacterial, antiprotozoan, and antifungal properties.

35.2 BIOACTIVE CONSTITUENTS

P. betle phytochemical screening showed that the plant is rich in vitamins, minerals, protein, enzymes, essential oil as well as bioactive compounds such as polyphenols, alkaloids, steroids, saponins, and tannins, etc. (Pradhan et al., 2013). Guha (2006) stated that the fresh green *P. betle* leaves contain 85–90% water, 3–3.5% protein, 0.4–1.0% fat, 2.3–3.3% minerals, 0.5–6.10% carbohydrate, 0.63–0.89 mg/100 g nicotinic acid, 0.005–0.01% vitamin C, 1.9–2.9 mg/100 g vitamin A, 10–70 μg/100 g thiamine. The bioactive constituents are mainly isolated from the leaves extracts, and the essential oil. Compounds like alkaloids, fatty acids, phenolics, alcoholic compounds, flavonoids, terpenes, coumarin, and organic acids were obtained from the leaves extract. Kumari and Rao (2014); and Rekha et al. (2014) showed the presence of the tannins, anthraquinones, flavonoids, alkaloids, terpenoids, saponins, cardiac glycosides, glycosides, phlobatanins, hydroxychavicol acetate, allylpyrocatechol piperbetol, isoeugenol, anethole, stearic acid, methyl eugenol, carvacrol, chavicol, and allylpyrocatechol in leaf extract. The dried ethanol extracted *P. betle* leaves which were extracted by Ali et al. (2018) by ultrasound-assisted extraction reported the presence of

the compound like hydroxychavicol, eugenol, isoeugenol, and 4-allyl-1,2-diacetoxybenzene, allylpyrocatechol 3,4-diacetate. Atiya et al. (2017) reported the presence of the 1-n-dodecanyloxy resorcinol (H1) and desmethylenesqualenyl deoxycepharadione-A (H4) in the chloroform leaf extract of the var. Haldia by using nuclear magnetic resonance (NMR) analysis. Soxhlet extraction of *P. betle* leaves isolated the compounds like hydroxy chavicol, 4-chromanol and eugenol, 1-phenylpropene-3, 3-diol diacetate and 4-allyl-1,2-diacetoxybenzene (Muruganandam et al., 2017), Neophytadiene, propionic acid, and elemicin (Anugrahwati et al., 2016). Leaf extract using hexane, ethyl acetate (EA) and ethanol also showed the presence of the 4-allyl-1, 2-diacetoxybenzene, chavicol, and eugenol by the Choopayak et al. (2016). Solvent extraction (SE) and HPLC/ESI-MS–MS analysis by Ma et al. (2013) isolated the 3-ρcoumaroylquinic acid and 4-ρcoumaroylquinic acid, aqueous, and ethanol extract of leaves showed the 4-chromanol, phenol 2 methoxy 4-(-2 propenyl) acetate, eugenol (Deshpande and Kadam, 2013) and PBL extract showed the presence of the eugenol, a-tocopherol, b-carotene, hydroxychavicol, and ursolic acid (Rai et al., 2011) whereas crude aqueous extract showed the hydroxychavicol, hexadecanoic acid, octadecanoic acid, 2,3-bis(hydroxy)propyl ester, benzeneacetic acid, eugenol (Lakshmi and Naidu, 2010). Ghosh and Bhattacharya (2005*)* isolated the stigmast-4-en-3, 6-dione, allyl resorcinol, aristololactam A-II from the alcoholic extracts of the dried roots of the *P. betle* by the column chromatography.

The essential oil is another component of the *P. betle* extracted from the various cultivars and showed the range of the variations in different cultivars and stages of the plants' growth. *P. betle* is classified into different chemotypes based on the main component of its essential oil; for example, the Indian 'Sagar Bangla' cultivar is the Chavicol chemotype, the Isoeugenol chemotype is the Indian Piper betle 'Meetha' cultivar and Vietnamese betel sample Eugenol chemotype is 'Kapoori' cultivar and 'Bangla,' etc. (Satyal and Setzer, 2011). Arambewela et al. (2005b) found major constituents of the essential oil the *P. betle* were safrole and chavibitol acetate other compounds included p-cymene, 4-terpineol, eugenol, β-caryophyllene, and allylpyrocatechol diacetate. Apiwat et al. (2006) found 4-allyl-2-methoxy-phenolacetate (31.47%), 3-allyl-6-methoxyphenol (25.96%), and 4-allylpheny acetate (5.21%) with other minor compounds. Basak and Guha (2015) found 46 compounds among with major compounds like chavibetol (22.0%), estragole (15.8%), β-cubebene (13.6%), chavicol (11.8%), and caryophyllene (11.3%). The chemical structure of some vital compounds of *Piper betle* are given in Figure 35.1.

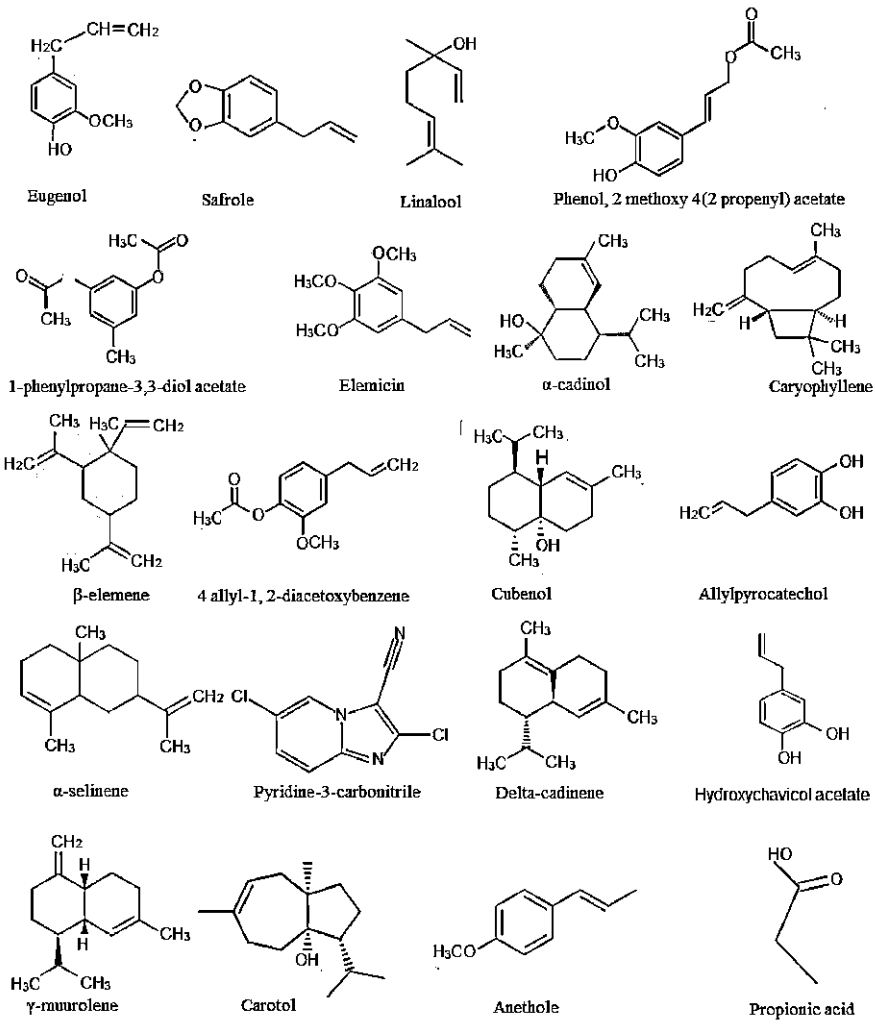


FIGURE 35.1 Chemical structure of important compounds of *Piper betle* L.

35.3 PHARMACOLOGY

35.3.1 ANTIMICROBIAL ACTIVITY

It is the most widely studied pharmacological activity of the *P. betle*, extracts, and essential oil inhibited the range of the microbes. Leaf extract showed activity against several gram-negative and gram-positive bacteria

(Nouri and Nafchi, 2014). Ether leaf extract showed activity against the *Aspergillus flavus* (Parmar et al., 1998), aqueous, and methanol leaf extract showed activity against 10 gram-positive, 12 gram-negative bacteria and one fungal strain, *Candida tropicalis* (Nair and Chanda, 2008). Trakranrungsie et al. (2008) showed that the ethanol leaf extract showed activity against zoonotic dermatophytes such as *Candida albicans, Microsporum canis, Microsporum gypseum,* and *Trichophyton mentagrophyte*, Ali et al. (2010) also showed the antimicrobial activity of the aqueous leaf extract using chloroform against 124 fungal strains. Ethanol, EA, acetone, and Dichloromethane leaves extract showed activity against the *Staphylococcus aureus* (Taukoorah et al., 2016), methanol, and acetone extract of leaves showed antibacterial activity against *Escherichia coli, Klebsella pneumoniae*, *Bacillus subtilis, Bacillus cereus, Salmonella typhi, Enterbactor aerogenes*, and *Staphylococcus aureus* (Jayalakshmi et al., 2014). Leaves extract showed the antibacterial activity against bacteria like *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus mutans*, *Streptococcus salivarius* (Ali et al., 2018), and *Vibrio alginolyticus* (Othman et al., 2018). Crude leaf essential oil of *P. betle* showed antibacterial activity against *E. coli, Pseudomonas aeruginosa, S. epidermidis, S. aureus, S. pyogens* (Arambewela et al., 2005a, b), and *Acinetobacter*, antibacterial activity against *Mycobacterium smegmatis, S. aureus,* and *Pseudomonas aeruginosa* (Madhumita et al., 2019). Essential oil showed antifungal activity against *Aspergillus flavus* and *Penicillium expansum* (Basak, 2018).

35.3.2 GASTROPROTECTIVE ACTIVITY

P. betle hot water leaves extract increased the mucus content of the gastric wall in the rats by which increases the gastric mucosa; however, it did not inhibit the acid secretion from the gastric mucosa. The gastroprotective activities of the higher dose of hot water extract were found significantly greater than Misoprostol, and the antioxidants play an important role in this gastroprotection (Arambewela et al., 2004; Pradhan et al., 2013).

35.3.3 ANTIOXIDANT ACTIVITY

The *P. betle* rich in polyphenolics, flavonoids, and tannins are free radicals quenching compounds; however, leaf phenolics of *P. betle* have less polarity than other phenolic antioxidants due to their high value of oil-water partition

coefficient (Rekha et al., 2014). Leaves extracts can effectively inhibit the lipid peroxidation (LPO) process and showed strong hydroxyl radical and superoxide anion radical scavenging activity compared to ascorbic acid and BHT (Pradhan et al., 2013).

35.3.4 ANTIDIABETIC ACTIVITY

The oral administrated hot water (HWE) and cold ethanolic extract (CEE) of *P. betle* leaves lowered the blood glucose level in normoglycemic and streptozotocin (STZ)-induced diabetic rats. Both extracts also reduced the external glucose load in the normoglycemic rats. The antidiabetic activity of HWE is comparable to that of CEE. Moreover, HWE failed to inhibit the glucose absorption from the small intestine of rats (Arambewela et al., 2005b). Sujatha et al. (2011) also concluded that the capsule formed by the hot water extract by subsequent spray drying powder effectively treated type 2 diabetes.

35.3.5 IMMUNOMODULATORY ACTIVITY

Methanolic extract of the *P. betle* was examined for its effect on the immune system of the mice. The effects were studied in vitro on lymphocyte proliferation, interferon-gamma receptors, and nitric oxide (NO) production and *in vivo* on mice immunized with sheep red blood cells at different dose levels for the humoral and cellular immune responses. The extract abled to suppress the peripheral blood lymphocyte proliferation stimulated due to the phytohaemagglutinin. The possible immunosuppressive effect of the extract was suggested due to the reduction in antibody titer and increased suppression of inflammation effect of the extract on cellular and humoral response in mice (Kanjwani et al., 2008).

35.3.6 EFFECT ON THE CARDIOVASCULAR SYSTEM

The heart shape of the *P. betle* leaves indicated its natural role in promoting cardiovascular health, which was proved by various studies. The hydro-ethanolic extract showed cardioprotective potential against cardiac hypertrophy induced by isoproterenol in male albino Wistar rats. The extract was able to counter the levels of glucose, protein, albumin, lipid profiles (total cholesterol, HDL, and triglycerides), urea, creatinine, cardiac maker enzymes, reduced enzymatic antioxidants, and serum to normal and repairment of cellular

architecture of the heart (Doss et al., 2019). Aqueous juice extract of *P. betle* also showed such protection in isoproterenol induced cardiac hypertrophic rats (Doss et al., 2020), *P. betle* EA extract promoted the cardioprotection by strengthening the antioxidant defense system (Savsani et al., 2020).

35.3.7 HEPATO-PROTECTIVE ACTIVITY

P. betle leaf extracts inhibited the increased level of the aspartate aminotransferase and alanine aminotransferase activities due to the liver injury induced by the carbon tetrachloride (CCl_4) in a rat model. It also attenuated total glutathione S-transferase (GST) activity and GST alpha isoform activity, and on the other hand, enhanced superoxide dismutase (SOD) and catalase (CAT) activities. The extract protected the liver by decreasing alpha-smooth muscle actin (alpha-SMA) expression, inducing active matrix metalloproteinase-2 (MMP2) expression through the Ras/Erk pathway, and inhibiting TIMP2 level that consequently attenuated the fibrosis of the liver (Young et al., 2007).

35.3.8 RADIOPROTECTIVE ACTIVITY

Ethanol extract of *P. betle* showed radioprotective activity *in vitro* in rat liver mitochondria and pBR 322 plasmids DNA. The extract prevented LPO and DNA strand breaks induced by the γ-ray effectively in a concentration-dependent manner (Bhattacharya et al., 2005).

35.3.9 CHOLINOMIMETIC EFFECT

The *P. betle* aqueous and EA leaf extracts showed cholinergic responses in isolated guinea-pig ileum, and the spasmogenic activity was observed higher in water than EA extract. Both types of extracts inhibited K^+ induced contraction in isolated rabbit jejunum possibly due to calcium channel antagonist constituents in the leaves of the *P. betle* (Gilani et al., 2000).

35.3.10 ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY

Analgesic activity of the methanolic leaves extract (MPBL) of *P. betle* evaluated by a hot plate, writhing, and formalin tests and anti-inflammatory activity using carrageenan-induced hind paw edema model *in vivo* in Swiss albino mice. The extract produced a significant increase in pain threshold

in the hot plate method whereas decresed significantly the number of licks induced by formalin and the writhing caused by acetic acid. The same ranges of doses of MPBL caused significant inhibition of carrageenan-induced paw edema after 4 h in a dose-dependent way (Alam et al., 2013).

35.3.11 ANTIDEPRESSANT ACTIVITY

Antidepressant activity of *P. betle* leaves ethanolic extract on adult albino mice (Swiss strain) was determined by Vinayak et al. (2012). The extract showed a significant antidepressant effect in all used doses, as indicated by reducing the duration of immobility compared to the control. The antidepressant effect was higher at 100 mg than at 200 mg. In addition, the impact at 100 mg was greater than that of imipramine.

35.3.12 ANTIFERTILITY ACTIVITY

P. betle petiole ethanolic extract treatment caused a reduction in reproductive organ weights, circulating estrogen levels, fertility, number of litters, serum glucose concentration, enzyme activity of acid phosphatase, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) compared to control value in normal cyclic female albino rats. Withdrawal of phyto-drug for 30 days restored completely/partially decreased reproductive organ weights, circulating estrogen levels, fertility, number of litters, the concentration of glucose, and enzyme activity of acid phosphatase SGOT and SGPT to control values (Sharma et al., 2007).

KEYWORDS

- **betel leaf**
- **bioactives**
- **ethanolic extract treatment**
- **gastroprotective activity**
- **pharmacology**
- ***Piper betle***
- **serum glutamic pyruvic transaminase**

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CHAPTER 36

Pharmacological Activities of Bioactive Compounds from the Aromatic herb *Piper trioicum* Roxb.

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36.1 INTRODUCTION

The aromatic plants of the genus *Piper* are cosmopolitan in distribution with nearly more than 1,000 species employed as food commodities and valued as traditional medicine. *Piper trioicum* Roxb. belongs to the Piperaceae family, which was distributed in South Asian countries. It is generally known as Toka miriyalu in Telugu, Canarsie pepper in English, This whole plant shows medicinal values like rubefacient, diuretic, hepatoprotective, and used for diabetes, muscular pains, headache, toothache, and cholera in folk medicine; the root is used as a diuretic agent (Sathis Kumar et al., 2011a).

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Piper trioicum is a slender climber. Leaves broadly ovate to elliptic-ovate, 9–13 by 5–9 cm, base rounded or oblique, apex acuminate, clearly 7-nerved from base, thick-chartaceous. Male spikes slender, to 18 cm long; female spikes to 20 cm long. Berries ellipsoid, ripening yellow (https://indiabiodiversity.org/species/show/263777). *Piper trioicum* plant is commonly found in Indo-Malaysia.

36.2 BIOACTIVES

The phytochemical studies revealed that extracts of *Piper trioicum* had shown the presence of alkaloids, steroids, flavonoids, phenolic compounds, carbohydrates, tri-terpenoids, tannins, and glycosides (Sathis Kumar et al., 2011a). Other reports have demonstrated that the *Piper trioicum* the ethanolic extract is rich in bioactive phytochemicals and has inhibitory activity on the amylase and lipase thus suggesting that the extract might be useful to limit dietary fat, glucose absorption, and the accumulation of fat in adipose tissue (Figures 36.1–36.3).

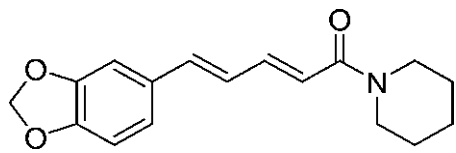


FIGURE 36.1 Structure of piperine.

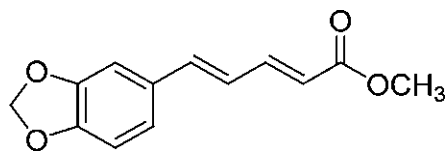


FIGURE 36.2 Structure of methyl piperate.

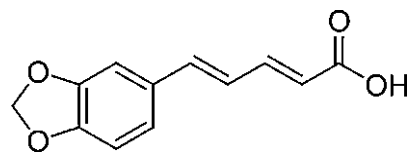


FIGURE 36.3 Structure of piperic acid.

36.3 PHARMACOLOGY

36.3.1 NOOTROPIC ACTIVITY

Nageswara Rao et al. (2013) studied the nootropic activity of a methanolic extract of the *Piper trioicum* against Scopolamine induced Wistar albino rats. These rats underwent maze trained for 15 days, then subjected to transfer latency (TL) by induce scopolamine of these rats, then treated with both standard Piracetam 200 mg/kg and methanolic extract of *Piper trioicum* (PT) (200 and 400 mg/kg) of those subjected rats. The Nootropic activity of methanolic extracts of PT shows more significant results than that of standard piracetam. Results are observed in rats which is dose-dependent, it shows significant improvement in cognitive function in rats with doses of 200 mg/kg and 400 mg/kg. The degree of percent reduction was more in rats receiving 400 mg/kg of extract.

36.3.2 ANTIBACTERIAL ACTIVITY

Nageswara Rao et al. (2013) evaluated the antibacterial activity of methanolic extract of *Piper trioicum* on Gram positive bacteria (*Staphylococcus aureus, Bacillus subtilis, Acinetobacter baumannii*) and Gram negative bacteria (*Escherichia coli, Proteus mirabilis, Salmonella typhi, Pseudomonas aeruginosa*). Different concentrations of extracts equivalent to 100, 200, and 400 mcg/ml were prepared. About 10 mcg/ml concentration of ampicillin was prepared and used as standards to be studied along with test solutions for their zone of inhibition. The results concluded that all the test organisms were inhibited significantly, by methanol extracts in a dose-dependent manner as compared to the standard. Antibacterial activity of methanolic extract of PT was more effective in *Escherichia coli* than other gram-positive and gram-negative bacteria, but there is no action against *Proteus mirabilis.*

36.3.3 ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY

The anti-inflammatory and analgesic potency of *Piper trioicum* (aerial parts) of ethanolic extract (EEPTs) was evaluated in carrageenan-induced rat paw edema and acetic acid-induced writhing model. Mallikarjuna et al. (2012) used two different dose levels (100 mg/kg and 200 mg/kg) and the results are compared with the standard drug Diclofenac (10 mg/kg). The percentage

inhibition of edema at dose 200 mg/kg at 30, 60, and 90 min were 37.50%, 48.71%, and 60.52%, respectively. It was found that the extract has anti-inflammatory activity in a dose-dependent manner, but EEPTs at 200 mg/kg showed a little higher anti-inflammatory activity than with that of standard drug Diclofenac. The percentage of inhibition of writhing of EEPTs at dose 100 and 200 mg/kg was found to be 53.46% and 62.30%, respectively. EEPTs show a little higher percentage of inhibition of writhing 62.30% when compared to the percentage of inhibition of writhing of Diclofenac was found to be 76.58% (Mallikarjuna et al., 2012).

36.3.4 ANTI-LIPID PER OXIDATION ASSAY AND MDA QUANTIFICATION

Sathis Kumar et al. (2011b) studied the anti-lipid peroxidation activity by *in vitro* method. The evaluation was done by measuring the malondialdehyde (MDA) of tissue homogenates; using ethanolic extract of *Piper trioicum* at different concentration dose levels 2,000, 1,500, 1,000, and 500 µg/ml, and good responses have been recorded in experimental results. The ethanolic extract of the plant is able to reduce thiobarbituric acid-reactive substances (TBARS) significantly when compared with a standard antioxidant ascorbic acid (1,000 µg/ml). The most significant action against lipid peroxidation (LPO) was observed at 1,500 µg/ml level.

36.3.5 INHIBITORY OF DIGESTIVE ENZYMES ACTIVITY

Sathis Kumar et al. (2010) investigated the inhibitory effects on the active enzymes by *Piper trioicum* that were extracted in ethanol. The extract was assayed for the measurement of inhibitory effects by the in-vitro method. Ethanolic extract of *Piper trioicum* was used in various concentration levels (2,000 µl, 1,500 µl, 1,000 µl, 500 µl). The results showed maximum amylase inhibition activity at 1,000 mcg/ml and lipase inhibition activity at 2,000 mcg/ml when compared with standards 100 U/L and 450 U/L, respectively. The alpha-glucosidase activity was increased with an increase in concentration levels of ethanolic extract of PT. *Piper trioicum* has significant inhibitory activity against amylase, lipase, and alpha-glucosidase.

36.3.6 IN VITRO ANTIOXIDANT ACTIVITY

Aparna Lakshmi et al. (2011) assessed the antioxidant activity of ethanolic extract of *Piper trioicum* by *in vitro* assay methods using DPPH (1,1-diphenyl-2-picrylhydrazyl) stable free radical scavenging, nitric oxide (NO) scavenging, hydrogen peroxide (H_2O_2) scavenging activities, reducing power, and total antioxidant status. From the above methods, the ethanolic extract of *Piper trioicum* in aerial parts of the plant has shown good antioxidant properties.

KEYWORDS

- **alpha-glucosidase activity**
- **anti-inflammatory**
- **antioxidant activity**
- ***in vitro* assay methods**
- **malondialdehyde**
- **nitric oxide**
- ***Piper trioicum***

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CHAPTER 37

Bioactives and Pharmacology of *Psidium guajava*

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37.1 INTRODUCTION

Psidium guajava L. (Guava), commonly known as Poor Man's Apple, is a member of the Myrtaceae family. The fruit-yielding trees grow up to an average height of 9.2 m. It is native to Central America and has been introduced to several parts of the world. The stem of the tree has a smooth peeling bark. The young stem is 4-angled. Leaves may be elliptic-oblong, base rounded to obtuse-cuneate, apex acute-apiculate, hirsute on both sides when young, and glabrous on aging except the nerves. Flowers are white and are seen as axillary cyme on the stem.

The fruits of *P. guajava* are edible, and fully ripened fruit is known to have a sweet and strong smell. The fruit is a globose berry crowned by persistent calyx lobes. In addition to the nutritional and health benefits that they carry, the fruits are popular due to their long shelf life, taste, and versatility in consumption.

37.2 BIOACTIVES

37.2.1 LEAVES

Leaves of *P. guajava* contain essential oil with the main components being α-pinene, β-pinene, limonene, menthol, terpenyl acetate, isopropyl alcohol,

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longicyclene, caryophyllene, β-bisabolene, cineol, caryophyllene oxide, β-copanene, farnesene, humulene, selinene, cardinene, and curcumene (Zakaria and Mohd, 1994; Li et al., 1999). Flavonoids and saponins combined with oleanolic acid have also been isolated from the leaves (Arima and Danno, 2002). Nerolidiol, β-sitosterol, ursolic, crategolic, and guayavolic acids have also been identified (Iwu, 1993). In addition, the leaves contain triterpenic acids as well as flavonoids like avicularin and its 3-L-4-pyranoside with strong antibacterial action (Oliver-Bever, 1986), 6% fixed oil, 3.15% resin, and 8.5% tannin, and several other fixed substances, fat, cellulose, tannin, chlorophyll, and mineral salts (Nadkarni and Nadkarni, 1999). The leaves of *P. guajava* is reported to have guavanoic acid, guavacoumaric acid, 2a-hydroxyursolic acid, jacoumaric acid, isoneriucoumaric acid, asiatic acid, ilelatifol D and β-sitosterol-3-0-B-D-glucopyranoside (Begum et al., 2002). In mature leaves, the most significant concentrations of flavonoids were found in July: myricetin (208.44 mg/kg), quercetin (2883.08 mg/kg), luteolin (51.22 mg kg^{-1}), and kaempferol (97.25 mg/kg) (Vargas-Alvarez et al., 2006). Two triterpenoids, 20ß-acetoxy-2a.3B-dihydroxyurs-12-en-28-oic acid (guavanoic acid), and 20,3B-hydroxy-24-p-coumaroyl oxy urs-12-en-28-oic acid (guavacoumaric acid), along with six known compounds 2a-hydroxyursolic acid, jacoumaric acid, isoneriucoumaric acid, asiatic acid, ilelatifol D and β-sitosterol-3-0-β-D-glucopyranoside, have been isolated from the leaves of *P. guajava*.

37.2.2 BARK

The bark of *P. guajava* contains 12–30% of tannin (Burkill, 1997), resin, and calcium oxalate crystals (Nadkarni and Nadkarni, 1999). They also contain minerals like calcium (0.30–1.00%), magnesium (0.06–0.30%), phosphorous (0.10–0.38%), potassium (0.21–0.39%), and sodium (0.03–0.20%). The fluoride concentration ranged from 0.02 ppm to 0.11 ppm, copper from 0.02–0.14 ppm, iron from 2.86–5.14 ppm, zinc from 0.31–0.57 ppm, manganese from 0.00–0.26 ppm, and lead from 0.00–0.11 ppm (Okwu and Ekeke, 2003). The presence of flavonoids, sesquiterpenes, alcohols, and acids triterpenoids has been reported by Hegnauer (1969).

37.2.3 ROOTS

Roots contain tannins, leukocyanidins, sterols, gallic acid, carbohydrates, and various salts. Root, stem, bark, and leaves contain a large percentage of tannic acid (Quisumbing, 1978).

37.2.4 SEEDS

The seeds contain 14% oil, dry weight with 15% proteins and 13% starch (Burkill, 1997), phenolic, and flavonoid compounds including quercetin-3-0-B-D-(2′-O-galloyl-glucoside)-4-0 vinyl propionate (Michael et al., 2002). Some isolated compounds are cytotoxic (Salib and Michael, 2004).

37.2.5 FLORAL BUD

Floral buds have the highest concentrations of myricetin (256 mg/kg), quercetin (3,605 mg/kg), luteolin (229 mg/kg), kaempferol (229 mg/kg) and apigenin (252 mg/kg) (Vargas-Alvarez et al., 2006).

37.2.6 FRUIT

The fruits of *P. guajava* are characterized by a low content of carbohydrates, fats, and proteins and by a high-water content (84.9) (Medina and Pagano, 2003). The pulp and peel of the fruit have shown a high dietary fiber content ranging from 48.55% to 49.42% and extractable polyphenols 2.62–7.79%. Verma et al. (2013) identified 43.21% dietary fiber and 44.04 mg GAE/g of phenolics. The presence of polyphenols such as tannins, phenolics, and flavonoids has also been reported in guava fruits. Guava is also an essential source of tryptophan (Bernadino-Nicanor, 2001). In guava fruits, proteinaceous compounds range from 0.4% to 2.6%, while fat ranges from 0.1% to 0.5% (Mandal et al., 2009).

The fruits are rich sources of vitamin A and vitamin C. Vitamin B complex, vitamin E, and vitamin K are also seen in moderate amounts. B-carotene is a common precursor of vitamin A. It ranges between 0.13 and 2.54 mg/per 100 g of guava fruit. The variability in coloration of the pulp depends on the beta-carotene level. The red-pulp guava contains gamma-carotene, beta-cryptoxanthin, lutein, rubixanthin, cryptoflavin, phytofluene neochrome, and lycopene (Jordan et al., 2003). Sharma et al. (2010) identified several carotenoids: lycopene, α-carotene, β-carotene, zeinoxanthium, 5,6,5,'6-diepoxy-ß-carotene, and 5,8-epoxy-3,3' 4-trihydroxy-β-carotene, which are rich in vitamin A. Mercadante et al. (1999) isolated 16 carotenoids from the flesh of Brazilian red guavas. Lycopene is another pigment that ranges from 0.04 to 4.04 mg/100 g in fruit.

37.3 PHARMACOLOGY

37.3.1 ANTI-MICROBIAL ACTIVITY

Aqueous and organic extracts of guava leaves have been reported to have antibacterial activity against *Staphylococcus aureus* (Anas et al., 2008; Milyani, 2012). Aqueous chloroform, methanol, acetone extracts of leaves, and essential oils (EOs) showed potential inhibitory activity against gram-positive and gram-negative bacteria. Reports on inhibitory effects of leaf extracts against different bacterial species of *Staphylococcus, Escherichia, Proteus, Shigella, Enterobacter*, and fungal species of *Candida, Arthrinium, Chaetomium* are available (Fernandes et al., 2014; De Arjau et al., 2014; Nisha et al., 2011; Nair and Chanda, 2007; Dhiman et al., 2011; Jaiarj et al., 1999; Sato et al., 2000). Guava leaf extracts have also been reported to control the entry and growth of the Influenza virus (Sriwilaijaroen et al., 2012). The reason for guava antiviral activity is protein degradation of guava extract (Puntawong et al., 2012). *P. guajava* showed a curative effect on infantile rotaviral enteritis (Wei et al., 2000). Anti-fungal properties have been studied by Padrón-Márquez et al. (2012). The acetone and methanol extracts of leaves displayed activities against dermatophytic fungi and hence can be used against skin disease. Phenols from the leaves were tested on human skin fibroblast cells, revealing antifungal properties (Suwanmanee et al., 2014). Conclusively, the leaves, seeds, skin, and guava pulp have displayed remarkable anti-microbial activity (Puntawong et al., 2012).

37.3.2 ANTIOXIDANT ACTIVITY

Free radicals produced in the body are the major reason for the oxidative damages, and hence possessing significant antioxidant activity indicates the reduction in such damages. Several reports suggest that copious amounts of polyphenols in *Psidium guajava* help in scavenging the free radicals. (Kimura, 1985; Okuda, 1982; Yan et al., 2006; Ryu et al., 2012; Roy et al., 2006; Ojewole, 2007; Wang et al., 2007, Ojan and Nihorimbere, 2004; Musa et al., 2011; He and Venant, 2004; Thaipong et al., 2005).

37.3.3 HEPATOPROTECTIVE ACTIVITY

The leaf extracts of *P. guajava* show a significant hepatoprotective effect. The methanolic extracts of *Psidium* is found to reduce the elevated serum

level and bilirubin in case of acute liver injury (Roy and Das, 2010). Pretreatment with asiatic acid, a triterpenoid extracted from the leaves and fruits, significantly blocked lipopolysaccharide (LPS), thus improving nuclear condensation, ameliorated proliferation, and less lipid deposition (Gao et al., 2006). The hepatoprotective activity of ethanolic extract of *P. guajava* was evaluated by Priscilla and Milan (2010). Several studies have indicated the ability of guava to reduce several parameters associated with liver injury (Roy et al., 2006).

37.3.4 ANTI-HYPERGLYCEMIC ACTIVITY

The role of *P. guajava* bark, leaves, and fruits as an antidiabetic agent has been studied by several authors. Extracts of stem and bark in water and ethanol (Mukhtar et al., 2004, 2006) have significant effects in rats. Deguchi and Miyazaki (2010) reported that guava leaf infusions reduced postprandial glycemia and improved hyperinsulinemia in murine models.

37.3.5 ANTIDIARRHEAL EFFECT

Aqueous extract of *P. guajava* leaves been reported to reduce the severity of diarrhea in rodents (Ojewole et al., 2008). Galactose-specific lectin in methanol extract of leaves and ripe fruits was shown to bind to *E. coli* preventing its attachment to the intestinal wall, thus preventing infections resulting in diarrhea. Ethanol and aqueous extract of *P. guajava* leaves showed remarkable inhibition of diarrhea (Lutterodt, 1992; Tona et al., 1999).

37.3.6 ANTIPARASITIC ACTIVITY

Leaf acetone extract exhibited acaricidal and insecticidal activities (Zahir et al., 2010), and ethanol extract functioned as a trypanocide agent (Adeyemi et al., 2011). Kaushik et al. (2015) reported leaves as an antimalarial agent. Leaves were found effective in treating and prophylaxis of malarial parasites (Nundkumar and Ojewole, 2002). Anti-helminthic properties towards gastrointestinal nematodes have been found due to the presence of condensed tannins in guava plants (Jan et al., 2013).

37.3.7 CARDIOPROTECTIVE ACTIVITY

P. guajava extracts are found to possess cardioprotective activity against myocardial ischemia reperfusion injury in rats. It also reduces the systemic blood pressure and heart rates (Ojewole, 2005) and contracts aortal rings (Olatunji et al., 2007). The cardioprotective activity has also been reported by Rahmat (2004) and Yamishiro (2003).

37.3.8 ANTICANCER ACTIVITY

An aqueous extract of *P. guajava* leaves inhibited the viability of the cancer cells in a dose-dependent manner (Chen et al., 2007). The EOs extracted from the leaves of *P. guajava* showed high anti-proliferative activity of human mouth carcinoma and murine leukemia (Manosroi et al., 2006). Anti-tumor effects of the methanolic extract were reported by Fernandes et al. (1995), acetone extract by Salib and Michael (2004), and aqueous leaf extract by Seo et al. (2005).

37.3.9 ANTI-INFLAMMATORY ACTIVITY

The aqueous extract of *P. guajava* leaves showed analgesic activity (Ojewole, 2006), while hexane, ethyl acetate (EA), and methanol extract of *P. guajava* leaves exhibited both analgesic and anti-inflammatory properties (Shaheen et al., 2000). The methanol extract of leaves showed antipyretic activity (Olajide et al., 1999). Muruganandhan (2001) has also reported on the anti-inflammatory properties of *P. guajava*. The essential oil significantly reduced edema formation (Kavimani, 1997). Laily et al. (2015) suggested using guava leaf as an immunostimulant agent as they modulate the lymphocyte proliferation response. Extracts derived from guava revealed immunomodulatory activities (Sen et al., 2015).

37.4 CONCLUSION

Researches have reported the presence of a wide variety of bioactive compounds in the leaf, seed, and bark of *P. guajava* that are capable of showing pharmacological properties with a beneficial effect on human health. An extensive search of literature available on *P. guajava* shows that

it is a popular and locally available remedy among various ethnic groups and ayurvedic practitioners for curing various ailments. Traditional claims should require experimental research to establish their efficacy. Thus, validation of medicinal use should be researched more extensively in clinical trials to prevent and cure various diseases. It is the need of the hour to find non-allopathic alternatives that reduce the risk factors of many chronic degenerative diseases, which helps in the treatment and thus decreases the socio-economic burden for the public health system. Further research should investigate the biodiversity of *P. guajava* and the purification of bioactive compounds to obtain active principles as alternative agents in therapeutic approaches.

KEYWORDS

- **anti-inflammatory activity**
- **bioactives**
- ***Escherichia coli***
- **guava**
- **methanolic extract**
- **pharmacology**
- ***Psidium guajava***
- ***Staphylococcus aureus***

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CHAPTER 38

Bioactives and Pharmacology of *Rauvolfia tetraphylla* L. (Family Apocynaceae)

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38.1 INTRODUCTION

Rauvolfia tetraphylla L. (devil pepper, be still tree) is a native plant of Caribbean islands and possibly the northern region of South America. However, it has been introduced and naturalized in many countries in South Asian and Australasian regions. It is a highly branched woody plant that flowers during summer and grows to about six feet in height. Among the different parts of the plant, root, and root extracts seem to be widely used in traditional medicine to treat a wide range of ailments (Rahman and Akter, 2016). Leaves are elliptic-ovate in shape, dark green in color, and distributed in whorls. Stems are more rounded with a rough, hairy, and outwardly greenish surface. Habitat of *R. tetraphylla* can vary remarkably as it is known to grow almost everywhere including near road-sites, wastelands, hills, lake banks, rocky cliffs, dry fields, etc. (Rao, 1956). Preparations of root, leaves, fruits, or a combination of more than one part of the plant has been shown to treat

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several adverse health conditions (Mahalakshmi et al., 2019). Efficacy of these traditional preparations in treating such a wide range of disorders and injuries is not clearly known. However, several phytochemicals, such as alkaloids, flavonoids, saponins, and tannins have been identified from the plant extracts, and several of these compounds may have therapeutic potentials.

38.2 BIOACTIVES

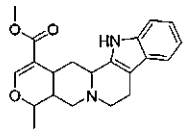
When compared to other *Rauvolfia* species, *R. tetraphylla* is particularly rich in phenolic and flavonoid compounds (Nair et al., 2012). At least 22 different alkaloids have been identified (Iqbal et al., 2013). Some of these alkaloids also include heterocyclic compounds with monoterpene indole skeletons (Gao et al., 2012) indicating *R. tetraphylla* produces a variety of monoterpenoid indole alkaloids (MIAs). Compounds identified include reserpine, serpentine, deserpidine, ajmaline, ajmalcine, yohimbine. These MIAs have been reported to possess significant pharmaceutical and biological properties. Biosynthesis of these compounds involve strictosidine substrate, formed by the condensation of tryptamine with secologanin. The monoterpenoid alkaloids identified in *R. tetraphylla* can be grouped into reserpine, ajmalicine, and ajmaline types of alkaloids (Kumara et al., 2019). Compared to alkaloid contents of other types of phytochemicals such as flavonoids, phenols, tannins, cardiac glycosides, saponins, and terpenoids were reported to be much lower (Vinay et al., 2019).

38.2.1 ALKALOIDS

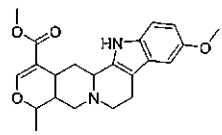
R. tetraphylla and related species are well known for their high content of MIAs and other alkaloids and are known for the production of indole alkaloids with novel skeletons via interesting biosynthetic pathways. Ajmalicine is a monoterpenoid indole alkaloid and found in root. Ajmaline is an indole alkaloid also isolated from the roots. Many of these alkaloids are grouped into yohimban and related alkaloid categories and many are also methyl esters. For example, aricine, and corynanthine are yohimban alkaloids. Deserpidine, raujemidine (an isomer of reserpine), raunescine, and isoraunescine are ester alkaloids (Iqbal et al., 2013, Mahalakshmi et al., 2019). Many of these alkaloids from *R. tetraphylla* have important pharmacological properties.

38.2.2 OTHER PHYTOCHEMICALS

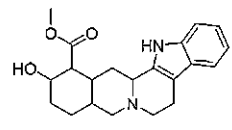
Compared to alkaloids reports on the presence of other types of phytochemicals such as flavonoids, terpenoids, phytosterols are scant. There was a report that identified a new labdane diterpene, (3β-hydroxy-labda-8(17),13(14)-dien-12(15)-olide) with an unusual γ-lactone moiety from air dried stems and branches of *R. tetraphylla* (Brahmachari et al., 2011). However, there are several studies that reported non-specific identification of flavonoids, terpenoids, saponins, cardiac glycosides, and phytosterols.



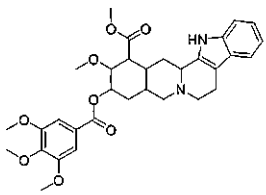
Ajmalicine



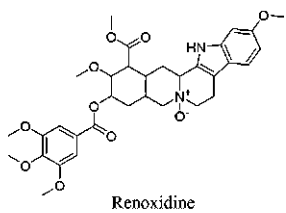
Aricine



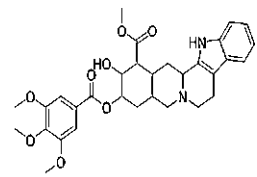
Corynanthine



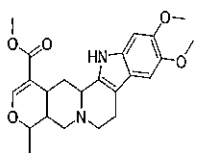
Deserpidine



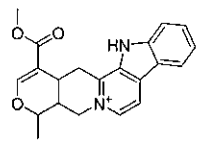
Renoxidine



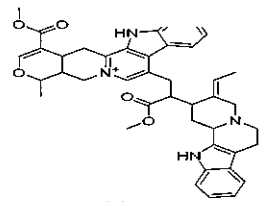
Raunescine



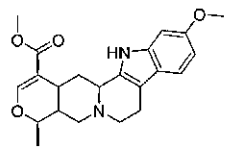
Isoreserpiline



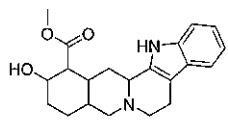
Serpentine



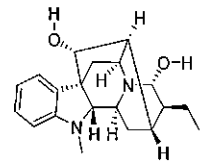
Serpentinine



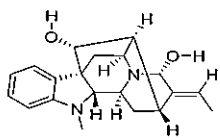
Tetraphylline



Yohimbine



Ajmaline



Ajmalan

38.3 PHARMACOLOGY

38.3.1 ANTIOXIDANT ACTIVITY

Extracts of various parts of the plant showed potent antioxidant activities. Methanolic extracts of dry leaves had high levels of total antioxidant capacity, 1,1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging activity, reducing power, and superoxide anion scavenging activity (Nair et al., 2012). There are also other studies that reported the antioxidant activities of leaf and extracts from other parts (Maheshu et al., 2010; Archana and Jeyamanikandan, 2015). Antioxidant activities of *R. tetraphylla* could be largely due to the rich presence of alkaloids. The MIA are in particular are produced in response to oxidative stress and were shown to be required for antioxidant responses in plants (Matsuura et al., 2014; Vera-Reyes et al., 2015). Reserpine was shown to possess antioxidant properties (Begum et al., 2012), however, it may induce comorbid pain, depression, and other neurological disorders (Naidu et al., 2006; Sousa et al., 2018). Among the different alkaloids tested yohimbine seems to be the most effective compound in terms of its antioxidant potential. In addition to serving as an antioxidant itself, it also enhanced the levels of endogenous antioxidants (Ansari and Khan, 2017). Antioxidant activity of the extracts of *R. tetraphylla* could also be in part due to flavonoids, terpenoids, saponins, and phytosterols that are present in the plants as several individual compounds belonging to these chemical families have antioxidant properties.

38.3.2 ANTIMICROBIAL EFFECT

Multiple indole alkaloids found in *R. tetraphylla* and their derivatives showed synergistic antimicrobial effects against drug-resistant *Escherichia coli* (Dwivedi et al., 2015). Ajmalicine was reported to produce antimicrobial effects (Das and Satyaprakash, 2018). In addition, Yohimbine also showed potent antibacterial activity (Özçelik et al., 2011). *In silico* studies provided evidence that reserpine has antibacterial activity against red complex pathogens, probably through its effects on transporters and efflux pumps that are important for bacterial cell survival (Ushanthika et al., 2019). Reduced drug (fluoroquinolone) susceptibility in the pathogen *Staphylococcus aureus*, was shown to be due to mutations in certain gene loci and multidrug efflux pumps. These efflux pumps can be inhibited by alkaloid reserpine, which

can be used in combination with antimicrobials to treat multidrug resistant infections (Schmitz et al., 1998).

In vitro antibacterial activity of ethanolic leaf extract of *R. tetraphylla* was studied by Abubacker and Vasantha (2011) against selected pathogenic bacteria *Bacillus cereus*, *Escherichia coli*, *Staphylococcus aureus* and *Yersinia enterocolitica* by disc diffusion assay. Bioactive compound reserpine was isolated from the leaf. The results revealed that the ethanolic leaf extract and reserpine compound are potent in inhibiting these bacteria, which cause gastroenteritis in human population.

38.3.3 ANTICANCER ACTIVITIES

Some phytochemicals in *R. tetraphylla* showed efficacy in controlling proliferation and promoting the death of cancer cell lines. For example, corynanthine boosted cytotoxicity in multidrug-resistant cancer cells (Zamora et al., 1988). Furthermore, ajmaline showed weak anticancer effects on human breast cancer cell lines, however, ajmalicine, yohimbine, and corynanthine had minimal or no anticancer effect (Xiuwei et al., 2007). Reserpine, another alkaloid from *R. tetraphylla*, also showed anti-cancer properties in drug resistant tumorigenic cell lines (Abdelfatah and Efferth, 2015). Instead of being the major cytotoxic agent in these cancer cells, reserpine perhaps acts as a chemosensitizer that increases the action of other chemotherapeutic drugs. However, another study showed a more direct chemotoxic effect, reactive oxygen species (ROS) mediated apoptosis, in non-small cell lung cancer cells (reserpine subdued non-small cell lung cancer cells via ROS-mediated apoptosis). Another alkaloid, serpentine may also have anticancer properties by targeting PI3Kγ, which enhances immune suppression during inflammation and tumor growth (Sharma et al., 2017). In addition, some yohimbine derivatives were efficient molecular targets for G-protein coupled receptors (GPCRs) that have a role in cancer pathogenesis (Paciaroni et al., 2020).

38.3.4 MUSCULAR EFFECTS

Phytochemicals, particularly alkaloids from *R. tetraphylla* show pharmacological effects on skeletal, cardiac, and smooth muscles. These effects are mediated by their actions on nicotinic, muscarinic receptors, and adrenoceptors. Plant alkaloids inhibited neuromuscular ileum and

diaphragm-phrenic-nerve synapses. In particular, serpentine competitively blocked muscarinic receptors whereas the precursor ajmalicine did not. Contractions in the diaphragm, regulated by nicotinic receptors, were completely inhibited by ajmalicine. Furthermore, serpentine also showed mild inhibition of the enzyme acetylcholinesterase (AChE) (Pereira et al., 2010). In accordance with these findings, another study showed ajmaline inhibited of Na^+ currents elicited from skeletal muscle (Körper et al., 1998). Ajmalicine, also known as raubasine and δ-Yohimbine, functions as an antagonist of postsynaptic α_1-adrenoceptors and thereby cause relaxation of smooth muscle. This pharmacological property allows its usage as an antihypertensive drug (Demichel and Roquebert, 1984). A related compound ajmaline increases the amplitude of spontaneous contractions in rat vascular smooth muscle (Patejdl et al., 2019). Furthermore, ajmaline also inhibited Na^+ and K^+ channel currents in skeletal muscle, with more inhibitory potency on K channel currents (Friedrich et al., 2007). The major therapeutic use of ajmaline though the treatment of arrythmia. Ajmaline specifically lowers intraventricular conduction and prolongs cardiac action potentials by inhibiting transient outward potassium currents (Obayashi et al., 1976; Bébarová et al., 2005). Corynanthine is another alkaloid found in the plant and it is a well-known α-1 adrenoceptor blocking agent. This compound produced a negative ionotropic effect on guinea pig papillary muscle and suppressed inhibited contractions of vascular smooth muscle (Godfraind et al., 1983; Kocić, 1994). Deserpidine has been used for the treatment of hypertension and also as a tranquilizer. Reserpine and deserpidine have been widely used for their antihypertensive action (Varchi et al., 2005).

38.3.5 EFFECTS ON NERVOUS SYSTEM

Among the different alkaloids from *R. tetraphylla* reserpine, raunescine, isoraunescine, reserpiline, and yohimbine were shown to produce pharmacological effects in the nervous system. When administered, reserpine elicits two major pharmacological outcomes, sedation, and gradual reduction in arterial blood pressure. Sedative effect of resperine is probably mediated via the reduction of the neurotransmitters 5-hydoxytryptamine and norepinephine (Alper et al., 1963). At a molecular level, reserpine showed high affinity for the vesicular monoamine transporter type-2 and blocked monoamine binding. These actions resulted in diminished vesicular storage and reduced release of monoamines into the synaptic cleft

(Sousa et al., 2018). Indeed, reserpine is both centrally and peripherally acting pharmacological agent producing its effects primarily by depletion of biogenic amines such as noradrenaline, dopamine, and 5-hydoxytryptamine. One notable central effect of reserpine is the production of severe depression as a side effect. Therefore, before the development of more effective drugs, reserpine was used as a tranquilizer to manage frantic psychotic patients, before being replaced by more effective drugs (Varchi et al., 2005). In addition to reserpine other alkaloids such as raunescine and isoraunescine also reduced norepinephrine levels in the brains of rats. In addition, raunescine also caused a reduction in the concentration of 5-hydroxytryptamine in rat brain (Paasonen and Dews, 1958). In an amphetamine induced hyperactive mouse model, oral administration of reserpiline, α-yohimbine as well as derivatives 11-demethoxyreserpiline and 10-demethoxyreserpiline produced remarkable antipsychotic action without any adverse extra pyramidal symptoms (Gupta et al., 2012). Yohimbine in particular has other central nervous system (CNS) effects. It has the modulatory capacity on alcohol addiction as it was shown to boost operant responding for sensory and conditioned reinforcers and promote relapse to alcohol-seeking in rats (Tabbara et al., 2020). Yohimbine also has pain reducing properties as it produced antinociceptive effects, mediated in part through the agonistic effects on 5-hydoxytryptamine (1A subtype) receptors in rats (Shannon and Lutz, 2000). In healthy humans, yohimbine induced mild anxiety and impulsivity, but these effects were more drastic in psychiatric patients, including mania in bipolar patients and drug craving in patients with addiction problems. Furthermore, yohimbine was shown to reduce high glucose utilization in lateral hypothalamus during electrical stimulation (Sun et al., 2010), suggesting that lateral hypothalamus is one of the important targets of CNS effects elicited by yohimbine (Mickley and Teitelbaum, 1979).

38.3.6 EFFECT ON THE SKIN

Skin is the largest organ of the body and various extracts of *R. tetraphylla* has shown to exhibit dermal protective effects. The major and prevalent skin disorders are acne, eczema, hives, ichthyosis, psoriasis, rosacea, seborrheic dermatitis, sunburn, and vitiligo. Various methanol, diethyl ether, benzene, ethanol, petroleum, ethyl acetate (EA), ether, chloroform extracts/juice from the leaves, stem, root, fruit, aerial parts, root, callus, and fruit has shown

to exhibit various dermal protective effects. The dermal protective effects are attributed to its antimicrobial, anti-inflammatory, and dermal protective properties. The different extracts obtained from various parts of *R. tetraphylla* has shown to protect against skin infection (against both gram-positive and gram-negative bacteria) activity. Furthermore, regarding the antimicrobial effects, the *R. tetraphylla* extracts exhibited anti-fungal effect (Nandhini and Bai, 2014, Suresh et al., 2008). The root paste of *R. tetraphylla* has shown to exhibit protection against head sores and other prevalent skin disorders (Ganesh and Sudarsanam, 2013; Panda et al., 2016; Ramakrishna et al., 2017).

38.3.7 OTHER TYPES OF EFFECTS AND ACTIVITIES

One major pharmacological application of yohimbine is its effectiveness in treating erectile dysfunction. Pharmacologically, yohimbine was shown to be a potent and selective α_2-adrenoceptor antagonist with much weaker α_1-antagonist effects. Yohimbine by inhibiting central α_2-adrenoceptors causes in a surge in sympathetic tone, along with an increase in blood pressure. Corpus cavernosum in humans and rabbits have postsynaptic α_2-adrenoceptors that upon exposure to agonists results in contraction. This effect is attenuated by yohimbine, which also suppressed norepinephrine induced contraction of corpus cavernosum (Tam et al., 2001). Erectile response stimulated by yohimbine may also involve antagonism of pre- and postsynaptic α_2-adrenoceptors. Norepinephrine release can be boosted by the antagonism of presynaptic α_2-adrenoceptors by yohimbine leading to higher activation of endothelial adrenoceptors and release of vasodilatory NO and prostanoids. High doses of yohimbine lead to increased blood pressure, mild anxiogenesis and frequent urination (Tam et al., 2001). In addition, there is one study that showed yohimbine averted cisplatin-induced renal toxicity via α_2-adrenoceptors mediated inhibition of cytokine expression (Tsutsui et al., 2018).

Traditionally, products from *R. tetraphylla*, such as extracts, pastes, decoctions, juices, and powders have been shown to alleviate a number of wide-ranging conditions such as gastrointestinal disorders, parasitic infections (anthelmintic), snake bites, and cardiovascular disorders (hypertension, myocardial infarction (MI)). With regard to the gastrointestinal tract, the extracts of *R. tetraphylla* exhibited anti-diarrheal and reduced gastrointestinal pain (Manna and Manna, 2016; Malaiya, 2016).

The anti-diarrheal activity may be due to its parasympathetic (cholinolytic, anti-muscarinic) effects and due to its antimicrobial action. The microbial infection can induce diarrhea and the increase in the cholinergic activity (parasympatho-mimetic), and this effect can increase the intestinal motility and induce diarrhea. The cardioprotective effect of *R. tetraphylla* occurs due to its ability to protect against MI and significantly lower the blood pressure, thereby exhibiting antihypertensive effects (Nandhini and Bai, 2015). Additionally, oxidative stress can drastically increase the risk of cardiovascular toxicity and thus leading to heart disease and increased blood pressure. *R. tetraphylla* has shown to possess significant antioxidant action and thus this protective effect can decrease the risk of cardiovascular diseases and lower the hypertension. Helminths/parasites are mainly classified as nematodes, trematodes, and cestodes. The clinically significant helminths/parasites are mainly present in the intestine (*Enterobius vermicularis* (pinworm), *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (roundworm), Ancyclostoma, and Necator species (hookworms), and *Strongyloides stercoralis* (threadworm)). Similar to the parasite-induced illness, snakes (bite) also induce morbidity and mortality. Snakes for their survival, to hunt a prey or for its own self-defense usually bites an animal or humans. These snakes (venomous and non-venomous) can cause lethal injury to humans. The snake venom can be cytotoxic (swelling and tissue damage), hemorrhagic (prevent clotting and induce bleeding), neurotoxic (cross the blood-brain barrier, affect the neurons/nerves in the central and peripheral nervous system), and myotoxic (break down muscles). Various extracts of *R. tetraphylla* has shown to protect against the toxic effects of parasites and snake-induced toxicity (Quattrocchi, 2012; Caamal-Fuentes et al., 2011; Choudhury et al., 2013). Efficacies in terms of symptomatic relief, side effects, cure rates, etc., are not well documented due to the very nature of traditional treatment methods (Iqbal et al., 2013; Mahalakshmi et al., 2019). These therapeutic effects may be mediated by anti-inflammatory, anti-microbial, anti-hypertensive, parasympathetic, and sympathetic modulatory, and central effects of phytochemicals present in this plant. Particularly, as discussed above, alkaloids alone are capable of eliciting all the therapeutic effects produced by the extracts and other products. Specific identification of flavonoids, tannins, saponins, and other classes of compounds remains largely incomplete and is an area for future studies.

KEYWORDS

- ***Rauwolfia tetraphylla***
- **reserpine**
- ***Escherichia coli***
- **monoterpenoid indole alkaloids**
- **pharmacological application**
- **phytochemicals**
- ***Staphylococcus aureus***

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CHAPTER 39

Phytochemical and Pharmacological Analysis of Black Rice (*Oryza sativa* L. indica)

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39.1 INTRODUCTION

The rice plants had been in use from ancient periods as food and medicine. The domestication of rice more than 8,000 years ago led to a series of developments in rice cultivation over millennia, making it the most important food item for many people in the world (Nene, 2005). The United Nations announced 2004 as an International Year of Rice (IYR). The main concept of IYR was 'Rice for Life,' which necessitates that rice, cereal is the primary source of food (Ahuja et al., 2007). The rice (*Oryza sativa* L.) crop is cultivated in many Asian countries like China, Thailand, Indonesia, and the Indian subcontinent. Rice has wide varieties, among which black rice has become popular as a medicinal food. Till now, 200 types of black rice varieties have been reported (Kushwaha, 2016). The ancient Indian palm-leaf manuscript mentioned the use of black rice seed powder for the treatment of jaundice, fibroids, wounds, and cancer (Chandramouli and Mallikarjuna, 2020). The

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synthesis of photochemical in black rice may vary from place to place as influenced by the local environment (Ito and Lacerda, 2019). The seeds are the main ingredients that contain good numbers of flavonoids that can scavenge free radicals (Ling et al., 2001). The presence of secondary metabolites in rice is regulated by postharvest treatments (Norkaew et al., 2017). The lion's share (62%) of global black rice production comes from China, followed by Srilanka, Indonesia, India, and the Philippines. The queen of cereal crops, black rice is rich in high carbohydrates, fat, fiber, protein, vitamins, minerals, fatty acids, and higher digestible enzyme contents (Verma and Srivastav, 2020).

39.1.1 REASONS FOR BLACK SEED RICE

The black color of these rice grains is due to the deposition of anthocyanins in the aleurone layer, seed coat, and pericarp (Chaudhary, 2003). The anthocyanins accumulate rapidly in the pericarp during seed development giving black rice a dark purple color (Abdel-Aal et al., 2006; Shao et al., 2011). These plants will reach a height of 31 to 45 cm, with 20–25 tillers having a bushy appearance. The morphological characters vary from variety to variety as influenced by the local environment. The black rice varieties are different from white rice varieties in having purple color anthocyanin pigments; hence, it is also named as 'purple rice.' The stems, leaf bases, ligules, and leaf tips show predominantly purple color. The life span of black rice ranges from 110–125 days, depending on its variety. The seeds are elongated and measure 1 cm in length and 1 mm in width. The black or purple color also appears on the fruit coat in a mosaic fashion, but the black rice without the seed coat is completely black in color. The pericarp and seed coat show diverse color shades due to pigment deposits. Colored rice is well known to have applications in indigenous systems of medicine. Black rice exists with different names in various countries like Forbidden and Purple rice, Japonica, Chinese, Indonesian, and Thai black rice varieties. All of them will have black-colored grain (Figure 39.1) (Kushwaha, 2016).



FIGURE 39.1 Black rice fields – close-up view of black rice plants and seeds.

39.1.2 DISTRIBUTION OF BLACK RICE IN THE WORLD

There are several varieties of black rice available today; these include Indonesian black rice, Philippine balatinaw rice (Philippine Rice Research Institute), and Thai jasmine black rice. In Bangladesh, it is known as Kalodhaner chaal (black paddy rice) and is used to make polao or rice-based desserts. Black rice food is known to contain high anthocyanin content than any other food item (Yao et al., 2013). Among different rice varieties, black rice gained more popularity in recent days. The studies on black rice varieties were started in Brazil in 1994 (Ito and Lacerda, 2019). It is cultivated and distributed in China, India, Thailand, and southeast Asian regions (Ling et al., 2002; Kong et al., 2008). The production of black rice is majorly (~62%) from China, Indonesia, the Philippines, and the Indian subcontinent countries. Thailand stands in the ninth position in black rice cultivation (Ichikawa et al., 2001; Sompong et al., 2011). This rice is the more popular staple food in Europe than in Southeast Asiatic countries (Simmons and Williams, 1997).

The *Oryza* genus contains 21 wild species. Studies have shown that Indo-China was the center for ancestral diversity of *Oryza rufipogon,* red or brown bread rice. *O. rufipogon,* red rice attains red color due to proanthocyanidin accumulation. Of the various species of wild rice, *Oryza granulata, O. nivara*, *O. officinalis,* and *O. rufipogon* occur in India. *Oryza nivara* and *O. rufipogon* have red grains, and both are used as food and medicine (Ahuja et al., 2007). The term *nivara* is derived from the Sanskrit root niv, which means fattening or nourishing. According to the ancient Indian texts on Ayurveda, *nivara* rice has the unique medicinal property of redressing any imbalances in the tridosha (Nene, 2005). This rice is widely used in Ayurvedic treatment and has the rare capability to enrich the body elements, to exclude toxic metabolites, to strengthen, regenerate, and energize the body, to regulate blood pressure, and to prevent skin diseases and premature aging (Ahuja et al., 2007). It is also eaten on the traditional days of fasting in many parts of India.

Popularly cultivated two white rice species are *Oryza glaberrima* and *O. sativa*. *O. glaberrima* is cultivated in some areas of Africa, where as *O. sativa* is very well distributed globally. The global pattern of rice cultivation and domestication is in consonance with human migration patterns (Ge and Sang, 2011). *Oryza sativa* has two major sub-varieties viz., var. *indica* and var. *japonica*. The geographical distribution of var. *indica* is tamed to Himalayan ranges, oriental India, Thailand, and Myanmar, but var. *japonica* is domesticated in China (Londo et al., 2006).

39.1.3 HISTORICAL BACKGROUND AND IMPORTANCE

In the ancient dynastic times of China (Newman, 2004), black rice was called 'emperors or forbidden rice' as it was meant to be used for royal family members of China and Indonesia only (Rao et al., 2006) and were believed it is having multiple functional food with good eating qualities and also comprises of medicinal properties (Kristamtini, 2009). It was often served along with fresh mangoes and lychees. This rice also became precious because of its low yield than white rice without anthocyanins (Chaudhary, 2003). Traditional Chinese and Taiwanese food contains black rice as dessert, sweet or savory dish and noodles. Recent trends reveal consumption of black rice is becoming more common owing to its high nutritive, medicinal, and organic food value (Kushwaha, 2016).

39.1.4 GENOMIC SIGNIFICANCE OF THE WHITE AND BLACK RICE

Defective allele in the Rc bHLH gene is found in most cultivated white rice (*Oryza sativa* L.) varieties (Kushwaha, 2016) and Black grain originated because of ectopic expression of the Kala4 bHLH gene in the promoter region (Oikawa et al., 2015; Kushwaha, 2016). Both Rc and Kala4 genes regulate the enzymes, chalcone synthase, dihydroflavonol-4-reductase and, leucoanthocyanidin reductase and dioxygenase genes to create anthocyanin pigments (Kushwaha, 2016). From the genome analysis, it was recognized the spread of black anthocyanin pigment in black rice is from tropical *japonica* variety to *indica* subspecies is attributed due to the alleles of Kala4 through many natural crossbreeding processes. Japanese researchers discovered that its genetic trait is traceable to a rearrangement in a gene called Kala4, which activates the production of anthocyanin, a water-soluble pigment which might show different colors depending on the pH. Oikawa et al. (2015) proved the involvement of Kala4 gene is accountable for the black color of the rice and its products.

39.2 MEDICINAL CHEMISTRY AND BIOLOGICAL ACTIVITIES OF BLACK RICE

Chinese medicine implicates black rice for kidney, long life, stomach, and liver diseases (Kushwaha, 2016). It is also considered as a blood tonic because of its rich iron. The consumption of this rice as a healthy food in Korea since ages reported (Medhabati et al., 2014). Traditional Chinese medicine explains that it is good for old people and as a tonic, and the Indonesians consider it as a

functional food (Pratiwi and Purwestri, 2017). According to Nepali hill farmers, black rice is good during "the maternal period." But while some cultures value black rice, in other places, such as Laos, it is viewed as nutritionally inferior to white rice. In India, black rice is indigenous to northeast India and is extensively grown in Assam and Manipur states. Assam is rich in the production of black rice (Hui et al., 2010). It is commonly eaten in Manipur because of its medicinal value, called *chak-hao,* which means delicious rice. This black rice is eaten during traditional feasts (Devi et al., 2017) in Manipur. *Chak-haokheer* is a popular pudding in these regions, and the water in which black rice is boiled is used in these parts to wash hair, in the belief that it makes hair strong. Black rice was consumed in Japan and China as a source of antioxidants and stress relievers (Ryu et al., 2000). The antioxidant properties of anthocyanins inhibit the formation of free radicals and help in reducing LDL cholesterol (Adom and Liu, 2002). The extracts of black rice remove superoxide anions more efficiently (Nam et al., 2006). It has been confirmed that dermal and wound pathogens' antibacterial activity was increased by colored rice (Pumirat and Luplertlop, 2013).

It has anti-inflammatory, anti-angiogenesis, and antiosteoporosis properties (Dias et al., 2017) and prevents invasion of cancer cells and induces differentiation, and is a step needed to prevent metastasis of cancerous cells (Luo et al., 2014). The recent work reveals that anthocyanins of black rice arrest the growth of breast cancer cells and have antimicrobial, antioxidant, antiarthritic, anti-inflammatory, cytotoxic, antidiabetic, hepatoprotective, and anticarcinogenic properties (Chandramouli and Mallikarjuna, 2018). Several studies have been conducted to select phytochemical-rich genotypes (Sompong et al., 2011) and to isolate and characterize bioactive compounds from black rice (Pang et al., 2018).

The grain color of the black rice is due to the accumulation of large quantities of anthocyanin pigments and proanthocyanidins deposited in the rice coat (Abdel-Aal et al., 2006; Huang and Lai, 2016; Ryu et al., 1998a, b; Yawadio et al., 2007). Anthocyanins are the flavonoid class of compounds that are potent antioxidants. The other compounds present are sterols, γ-oryzanol, tocopherols, tocotrienols, and phenolics like ferulic acid and *p*-coumaric acid, and diferulate in the pericarp and aleurone layer. In addition to this, it has higher levels of amino acids, proteins, vitamins, minerals, free fatty acids, and fatty acid methyl esters than white rice (Ito and Lacerda, 2019; Suzuki et al., 2004). The presence of minerals like phosphorus (P), manganese (Mn), iron (Fe), and zinc (Zn) depends upon the rice varieties and type of soil (Qiu et al., 1993; Liu et al., 1995). Tricin (flavonoid compound) is mainly observed in the bran or the fiber part of black rice (Duyi et al., 2017) and contains various

bioactive compounds with nutraceutical potentials such as antioxidant, antiviral, immunomodulatory, antitubercular, anti-inflammatory, and antitumor activities (Samyor et al., 2017). Black rice contains more vitamins B and E, niacin, calcium (Ca), Mn, Fe, and Zn than white rice (Suzuki et al., 2004). It is rich in fiber, and the grains have a nutty taste (Adom and Liu, 2002). The anthocyanins not only act as antioxidants, but they also activate detoxifying enzymes. Rice arrests the proliferation of cancerous cells by inducing the death of cancerous cells (apoptosis) (Adom and Liu, 2002).

The black rice has flavonols, flavones, isoflavones, luteolin, apigenin, quercetin, isorhamnetin, myricetin, and kaempferol (Verma and Srivastav, 2020). The important four anthocyanins such as cyanidin-3-*O*-galactoside, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside, and peonidin-3-*O*-glucoside were reported and have been quantified from black, purple, and red rice (Goufo and Trindade, 2014). The compounds cyanidin-3-*O*-rutinoside, cyanidin-3,5-diglucoside, malvidin-3-*O*-glucoside, γ-aminobutyric acid, peonidin-3-glucoside, and petunidin-3-glucoside accountable for the black color of the rice were concentrated more in black rice than other rice varieties (Prasad et al., 2019) however, most of the studies reported cyanidin-3-*O*-glucoside and peonidin-3-*O*-glucoside as the major compounds of the black rice (Ichikawa et al., 2001). The peonidin, peonidin-3-glucoside, and cyanidin-3-glucoside of black rice were reported to be a hindrance to cancer cell invasion (Chen et al., 2006). Phytochemical screening reported the presence of alkaloids, phenols, flavonoids, anthocyanins, tannins, and terpenoids without any traces of steroids (Moko et al., 2014). Phenols and anthocyanins are reported in methanolic extract of black rice from Thailand, China, and Srilanka (Sompong et al., 2011). High concentrations of seven anthocyanins were reported in dehulled Japanese black rice (Pereira-Caro et al., 2013) through the HPLC method. Similarly, the presence of alkaloids, flavonoids, phenols, terpenoids, glycosides, and tannins was reported in the methanolic extract of wild rice *O. rufipogon* (Devi and Yasodamma, 2016). Moko et al. (2014) reported alkaloids, flavonoids, phenols, and terpenoids without any traces of steroids from colored and non-colored white rice varieties from Indonesia. The structure and characterization of some phytosterols such as 24-methylene-ergosta-5-en-3β-ol, 24-methylene-ergosta-7-en-3β-ol, fucosterol, and gramisterol compounds and three triterpenoids, cycloeucalenol, lupenone, and lupeol from black rice are studied by GC-MS, LC-MS, and NMR. These compounds showed strong antileukemic activity (Suttiarporn et al., 2015). The gramisterol of black rice bran has showed anticancer activity significantly (Figure 39.2) (Suttiarporn et al., 2015).

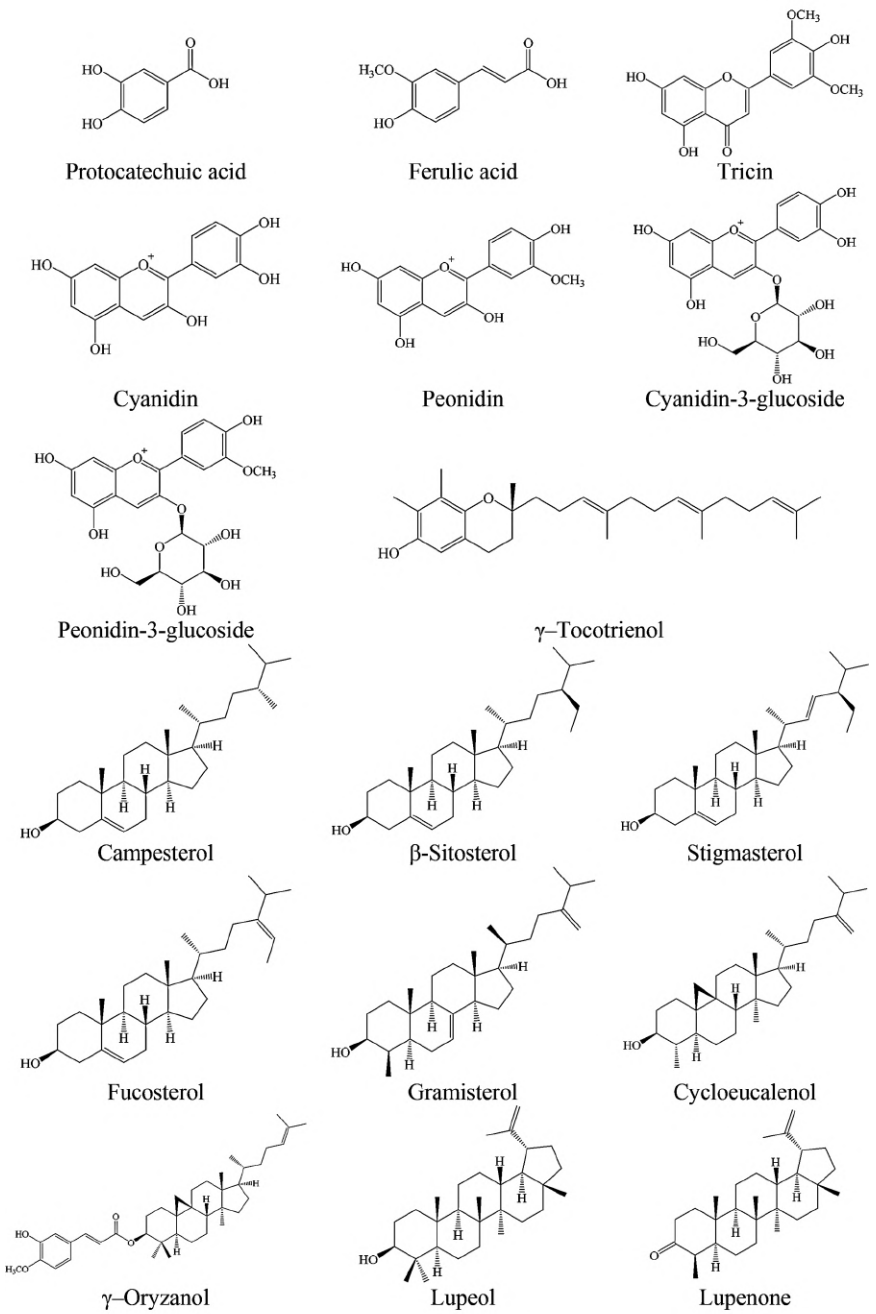


FIGURE 39.2 The chemical compounds isolated from the black rice.

39.3 CONCLUSION

The emerging human populations and diseases associated with them reiterate the need to look for alternative and orphan food sources. Black rice was considered as emperor's rice or long-life rice giving importance as food and medicinal benefits. It is a crop cultivated in several Asian countries like China, Thailand, Indonesia, and the Indian subcontinent. The black color of the grains is due to anthocyanins in the pericarp. Black rice is known to have various secondary metabolites that are responsible for diverse biological activities. The accumulating evidence indicates that black rice is a multifunctional nutraceutical food. Though the medicinal and health-promoting effects of black rice are known in many Asian countries, its full potential is yet to be explored in other parts for meeting global food and medical demand. Hence, efforts are to be taken to popularize the medicinal and food benefits of black rice in other parts of the world. In addition to this, wide varieties of black rice are to be developed through classical and non-classical approaches.

KEYWORDS

- **anti-angiogenesic**
- **antioxidants**
- **biological activities**
- **black rice**
- **flavonols**
- **isoflavones**
- **methanolic extract**
- ***Oryza sativa***

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CHAPTER 40

Bioactive Potential and Phytopharmacological Activity of *Abuta rufescens* Aubl.

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40.1 INTRODUCTION

The amazonian plant *Abuta rufescens*Aubl. is native to the Amazonian jungle, which is surrounded by rivers Napo, Ucayali, and Maranon in Brazil belonging to the family Menispermaceae (Swaffar et al., 2012). Its global distribution is in South America, Brazil, Peru, Bolivia, and Los Angeles (USA). It is the most rapidly growing genus in the American Menispermaceae family (Ruiz et al., 2011). *Abuta rufescens* Aubl. is a plant with edible thick leaves and grape-sized berries. The Shipibo-Conibo people used this Abuta to prepare arrows containing curare, an alkaloid and dart head poison (Bisset, 1992) that paralyzes the prey. Its decoction is used to treat stomach ulcers, liver pain, and diabetes mellitus (Arevalo, 1994).

This plant was shipped from French Guiana to Europe in the 1700s under the name "white pareira brava" for a preparation used to rid the liver,

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kidneys, and bladder obstructions such as mucus, grit, and sand. It was previously priced in the production of curare by various Amerindians (De Filipps et al., 2004).

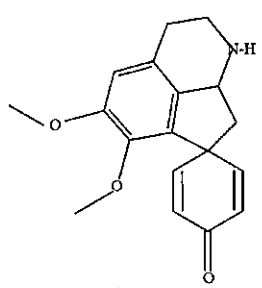
Abuta rufescens research had shown that abuta manages various problems related to the women physiology as it is also known as midwife herb in South America because it is used to treat various women problems such as menstrual cramps and is used as an emmenagogue (stimulates or increases menstrual flow), etc. It is used to prevent threatened miscarriage. It is also used to stop uterine hemorrhage after childbirth. It is used in minor reproductive tract conditions. It also purifies the blood and maintains hormones level in the blood. It is also used to increase vaginal discharge and improves fertility too. It is also used to increase sexual desires in some cases. It has abortion-inducing actions as well. It also acts as a milk cleanser for women (Mabberley, 1997).

A. rufescens is used for the treatment of various skin diseases such as acne, burns, itching, psoriasis, wounds, boils, or other various skin related diseases. *Abuta rufescens* is also used as antipyretic as it decreases body temperature during fever conditions and is also used to reduce pain as analgesics. It is used to treat respiratory tract infections such as bronchitis, cough, common cold, alveolar inflammation and Asthma (Triana and Planch, 1862).

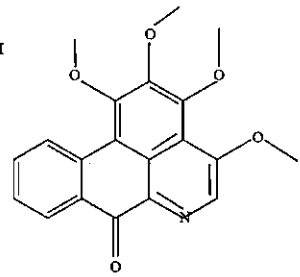
Expectorant activity is also reported of *Abuta rufescens*. It is widely used in expectorants preparations and helps in expelling out the mucus and phlegm from the mucus cavity or throat. *Abuta* preparations are used as an expectorant and help in expelling out the mucus and liquefies the phlegm thickness and due to which phlegm can be expelled out easily from the mucus cavity (Triana and Planch, 1862).

40.2 BIOACTIVE COMPOUNDS

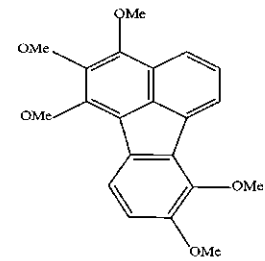
Several classes of alkaloid isolated from *Abuta* such as isoquinoline, benzylisoquinoline, benzyltetraisoquinoline, oxaporphine, bisbenzyltetraisoquinoline, aporphine, proaporphone, azofluoranthene, benzazepine, imeluteine, rufescine, stepharine alkaloid. There are four oxaporphine alkaloids found in it such as homomoschatoline, imenine, splendidine, grandirubrine (tropoloisoquinoline) (Menachery, 1996).



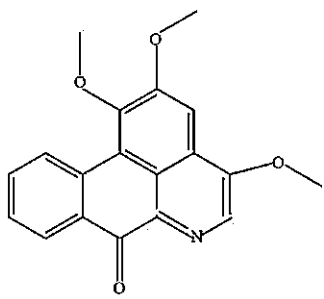
Stepharine



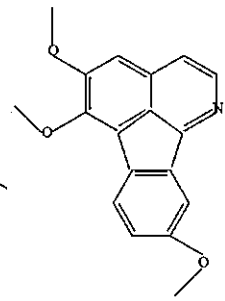
Imenine



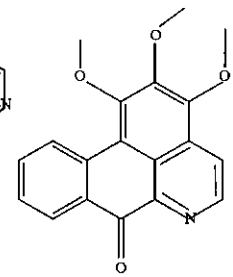
Imeluteine



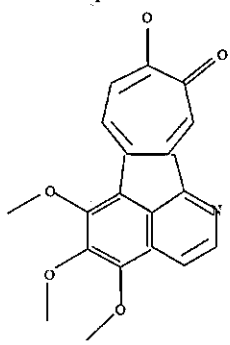
Splendidine



Rufescine



Homomoschatoline



Grandirubrine

40.3 PHARMACOLOGY

40.3.1 ANTI-CANCER ACTIVITY

Stepharine is also effective against human leukemic tumor cell lines such as K562 and U937. K562 cell lines related to chronic myelogenous leukemia are derived from a patient with blast crisis, and useful model for studies of differentiation towards erythrocytic, granulocytic, megakaryocytic lineages.

Another cell line U937 related to acute myelogenous leukemia, is a useful model for studies of differentiation with ATRA, TPA, AND 1,25 (OH) 2D3 inducing differentiation in to monocytic/macrophagic lineage. It is having DNA damaging properties as well (Giles et al., 2018).

40.3.2 MUSCLE RELAXANT AND ANTISPASMODIC ACTIVITY

Acetylcholinesterase (AChEs) inhibitors also called cholinesterase inhibitors to inhibit the breakdown of AChE into choline and acetate, thereby increasing both acetylcholine levels, and duration of activity in the central nervous system (CNS), as well as autonomous ganglions and neuromuscular junctions which are rich in acetylcholine. *Abuta rufescens* having muscle relaxant, antispasmodic action, which acts by inhibition of AChE enzyme activity and gives relief from muscle spasms (Naguib and Lien, 2010).

40.3.3 ANTI-LARVICIDAL ACTIVITY

Paludism (symptoms of malaria) is transmitted in nine Latin American countries that share the Amazon Forest region (Putz and Mooney, 1991). Some biological studies of *Abuta* have been reported to show anti-larvicidal activity (Ruiz et al., 2011). It shows anti-larvicidal activity against dengue caused by mosquito *Aedes aegypti* found in tropical zones (Roumy et al., 2007). Abuta's crude liquid alkaloid ethanolic extract is 66% effective as a weak-active parasite inhibitor (Garavito et al., 2006). It is also effective for *Plasmodium falciparum* chloroquine-resistant strain (FCR-5) and ferriprotoporphyrin inhibitory test with $IC_{50} < 10$ μg/ml (Ciccia et al., 2000).

40.3.4 CARDIOVASCULAR ACTIVITY

Cardiovascular activity is one of the important pharmacological activities shown by *Abuta*. This plant is widely used in hypertensive patients as it decreases blood pressure. It has also been reported to increase heart health by nourishing cardiac muscles. It is used to regulate the tone of the heart and the heartbeat of cardiac muscles (Putz and Mooney, 1991).

40.3.5 ANTIOXIDANT ACTIVITY

Most of the plant extracts of *Abuta rufescens* demonstrated significant antioxidant activity. It has been reported that *Abuta* having antioxidant

properties and it is used to stop free radical formation and prevents the body from harmful free radicals formed in the body due to various chemical reactions or physiochemical reactions (Desmarchelier et al., 1997).

40.3.6 HEPATOPROTECTIVE ACTIVITY

Investigations have shown the hepatoprotective activity of *Abuta rufescens* roots. *Abuta* roots are used as a hepatoprotective agent and protect the liver or hepatocytes from various toxicities and toxicity-causing chemical substances. Decoction or liquid prepared from the roots of *Abuta* is used as hepatoprotective (DeFilipps et al., 2004).

40.3.7 ANTIDIABETIC ACTIVITY

Abuta is also found to possess antidiabetic activity. Investigations have shown that imenine, an alkaloid found in abuta, act as a very potent antidiabetic agent. It maintains blood sugar levels in patients of diabetes mellitus. Insulin level is also regulated by imenine, so it is also known as an insulin management expert. The mechanism of imenine acts via combats free radicals causing damage to beta cells, so it is found as potent in curing Diabetes mellitus. It controls blood glucose levels while also preserving beta cell function. It reduces the symptoms of Diabetes mellitus, such as thirst, fatigue, hunger, urination, etc. Some of its activity also reported that it is also used to decrease diabetes-associated complications such as neuropathy, retinopathy, and nephropathy (Menachery, 1996).

KEYWORDS

- ***Abuta rufescens***
- **acetylcholinesterase inhibitors**
- **antidiabetic activity**
- **antispasmodic activity**
- **benzylisoquinoline**
- **ferriprotoporphyrin inhibitory**
- **hepatoprotective activity**
- **pharmacology**

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CHAPTER 41

Pharmacological Significance of *Solanum violaceum* Ortega

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41.1 INTRODUCTION

The therapeutic plant, *Solanum violaceum* Ortega (Family: Solanaceae), an auspicious curative plant, is essentially utilized as a vegetable (Islam and Islam, 2018). It is widely distributed throughout India and Bangladesh on forest edges, roadsides, and fallow lands (Karim et al., 2017; MPB, 2017). It is known in Bengali as 'Phutki,' 'Tit Begun,' 'Brihati Begun,' and 'Baikur.' The Marma community call it as 'Pokhongkhesi,' whereas 'Titbahal' by the Garo community in Bangladesh. 'Poison Berry' and 'Indian Night Shade' are the English designations of the plant.

As per World Health Organization (WHO), approximately 25% of plant species fill in as one of the significant wellsprings of present-day prescriptions (Islam et al., 2016). A persistent hunt is being made for the disclosure of novel particles to be utilized in the treatment of different illnesses or to ad lib existing treatment proposing *S. violaceum* plants are consistently an intriguing and promising wellspring of medications.

The entire plant or various parts of the *S. violaceum* plant have been utilized throughout the years for the cure of various sicknesses like cerebral pain, fever, heartburn, asthma, dry hack, fart, helminthiasis, dysuria,

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toothache, acid reflux, pruritus, diabetes, and ulcers, and so forth (Islam and Islam, 2018).

41.2 BIOACTIVES

S. violaceum plant contains different phytoconstituents having a place with alkaloids, starches, diterpenoids, flavonoids, glycosides, gum, phenols, proteins, saponins, and tannins (Raju et al., 2013; Karim et al., 2017; Mamatha and Palaksha, 2019). Various significant steroidal sapogenins and glycosides alongside different steroids have been segregated from this plant.

The MeOH concentrate of the air-dried products of *S. violaceum* was parceled between n-butanol and water, and afterward exposed to column chromatography (CC), prompting the seclusion of three pyridyl-type steroidal glycoalkaloids (1–3), one steroidal saponin, and two aglycones by acidic hydrolysis of 1–3, along with five referred to compounds recognized as two uncommon steroidal glycosides, indiosides An and F, two lignans, (1S,2S)-1-(4-hydroxy-3-methoxyphenyl)-2-[2-methoxy-4-[(2S,3R,4R)-tetrahydro-4-[(4-hydroxy-3-methoxyphenyl)methyl]-3-(hydroxymethyl)-2-furanyl]phenoxy]-1,3-propanediol, lariciresinol dimethyl ether, and a diterpene, ent-16α,17-dihydroxyatisan-3-one (Kaunda et al., 2021).

Complete phenolic content of methanolic concentrate of *S. violaceum* was found to be 54.67 gallic acid equivalent (GAE) per gram of dry concentrate (Raju et al., 2013). Fruits contain 1.8% steroidal alkaloids, while the leaves and roots contain steroidal alkaloids, solanine, solanidine, and solasodine (Ghani, 2003; Thongchai et al., 2010). Until this point, various steroidal sapogenins segregated from the ethereal pieces of *S. violaceum* incorporate indioside L, indioside M, indioside N and indioside O. Other steroids isolated from the plant are: (22E, 24R)-5α, 8α-epidioxyergosta-6,22-dien-3β-ol, (22E, 24R)-5α,8α-epidioxyergosta-6,9(11), 22-trien-3β-ol, 7-oxostigmasterol, 7-oxositosterol, diosgenin, yamogenin, diosgenone, and (25S)-neospirost-4-en-3-one. A lignin (for example, syringaresinol) and a coumarin (for example, scopoletin) were likewise detected in this plant (Chang et al., 2013). Steroidal glycosides, indioside G to K and some other molecules such as borassoside D, yamogenin 3-O-α-Lrhamnopyranosyl-(1→2)-β-D-glucopyranoside, borassoside E, 3-O-chacotriosyl-25(S)-spirost-5-en-3β-ol, sitosterol 3-Oβ-D-glucopyranoside, 7-hydroxysitosterol-3-O-β-Dglucopyranoside, N-p-coumaroyltyramine, trans-Nferuloyloctopamine, and tricalysioside U were also isolated.

The isolation and structural elucidation of four new compounds, namely indiosides L–O, along with 10 known (22E,24R)-5a,8a-epidioxyergosta-6,22-dien-3b-ol, (22E,24R)-5a,8a-epidioxyergosta-6,9(11),22-trien-3b-ol, 7-oxostigmasterol, 7-oxositosterol, diosgenin, yamogenin, diosgenone, (25S)-neospirost-4-en-3-one, syringaresinol, and scopoletin was carried out by Chang et al. (2013).

41.3 PHARMACOLOGY

The therapeutic plant, *S. violaceum* is for the most part utilized as a vegetable and contains various significant steroidal sapogenins and glycosides alongside different steroids. *Solanum violaceum* has promising organic and pharmacological exercises, including antinociceptive, antipyretic, injury recuperating, anthelmintic, antimicrobial, mitigating, antioxidant, and cytotoxicity. Consequently, *S. violaceum* is considered as a promising wellspring of lead compounds (Islam and Islam, 2018; Mamatha and Palaksha, 2019).

41.3.1 ANALGESIC ACTIVITY

Intense harmfulness was inspected for a time of seven days at dosages of 2.0 g/kg (i.p.) and 5.0 g/kg (p.o.) in mice. Pain relieving action (250 and 500 mg/kg, p.o.) was surveyed following acetic acid and hot plate-induced torment on mice model. In pain relieving tests, extract hindered 26% and 58% abdominal constriction at portions of 250 and 500 mg/kg, separately, and essentially raised agony limit at the two dosages (Mahaldar et al., 2016).

41.3.2 ANTHELMINTIC ACTIVITY

Live parasites *Paramphistomum cervi* Z. (Paramphistomatidae) and *Haemonchus contortus* R. (Trichostrongylidae) were utilized to assess anthelmintic action at groupings of 25, 50, 100, and 200 mg/mL. Quickest loss of motion happened in the two types of helminths at higher focuses (100 and 200 mg/mL). The overall list esteems for loss of motion in *H. contortus* were 1.69, 1.04, 0.57, and 0.31 at the pre-owned fixations. The overall record of death in *H. contortus* proposed that *S. violaceum* is parasiticidal at high fixation. Along these lines, *S. violaceum* is solid parasiticidal agent and practically identical with albendazole (Mahaldar et al., 2016).

41.3.3 ANTIOXIDANT ACTIVITY

The alcohol and high temperature water concentrates of *S. violaceum* showed antioxidant property, where the concentrates rummaged 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and showed lessening power limit just as, hindrance of linoleic acid peroxidation (Chiou and Chen, 2009).

41.3.4 ANTI-INFLAMMATORY ACTIVITY

The compounds isolated from *S. violaceum* was evaluated for its anti-inflammatory property (Yen et al., 2012).

41.3.5 ANTI-NOCICEPTIVE AND ANTIPYRETIC ACTIVITY

Karim et al. (2017) studied the antipyretic activities of *S. violaceum* and used methanolic extraction of leaf, fruit, and root in different concentrations and they found to reduce the rectal temperature. The study was made on the anti-nociceptive and antipyretic exercises of methanol extract of leaf (MELSV), fruit (MEFSV) and root (MERSV) of *S. violaceum* in Swiss albino mice. Anti-nociceptive action was assessed utilizing hot plate technique while antipyretic by brewer's yeast prompted hyperpyrexia. In the two tests, guinea pigs were partitioned into eight groups of six in each. The groups were treated as bad control (refined water), standard, and tests (250 and 500 mg/kg of MELSV/MERSV/MERSV). Diclofenac sodium (150 mg/kg) and paracetamol (150 mg/kg) were taken as guidelines for antinociceptive and antipyretic tests, individually. Every one of the medicines were administrated by means of oral gavages and uncovered that the plant extricates portion conditionally expanded maintenance time contrasted with the control groups. MELSV at 500 mg/kg essentially expanded maintenance time on the hot-pate of the guinea pigs than the MEFSV and MERSV treated groups. Both 250 and 500 mg/kg of MELSV and 500 mg/kg of MEFSV essentially diminished temperature to the test creatures 30, 60, 120 minutes in the antipyretic test. In surmising, the unrefined concentrates of *S. violaceum* showed against nociceptive and antipyretic exercises.

41.3.6 ANTI-BACTERIAL ACTIVITY

Raju et al. (2013) evaluated the whole plant extract of *S. violaceum* for its anti-bacterial activity. The plant extract uncovered most noteworthy action against *Aspergillus niger* (75%) and resistance to *Vibrio cholerae*.

The antibacterial activities of methanol extracts of *S. violaceum* plants was determined against the two Gram negative (*E. coli* and *Salmonella* spp.) and two Gram positive bacteria (*B. cereus* and *S. aureus*) showing the zone of inhibition. *E. coli* and *Salmonella* spp. showed the zone of inhibition with 3.02 ± 0.01 mm and 1.01 ± 0.03 mm, respectively. Similarly, *B. cereus* and *S. aureus* showed a zone of inhibition with 11.01 ± 0.02 mm and 15.11 ± 0.05 mm, respectively.

41.3.7 ANTI-FUNGAL ACTIVITY

The entire plant extracts of *S. violaceum* tested against *Candida albicans*, *Aspergillus niger*, and *Microsporum canis* showed a zone of inhibition 2, 3, and 2 cm, respectively (Raju et al., 2013). The antifungal actions of methyl alcohol (MA) extracts of *S. violaceum* plants was determined against two pathogenic fungi – *A. niger* and *C. albicans* showing the zone of inhibition 50.0% and 45.5%, respectively (Rana et al., 2014).

41.3.8 ANTI-HELMINTHES ACTIVITY

The methanolic extract of entire plant of *S. violaceum* utilized in contradiction of *Pheritima posthuma* and announced the impact of plant extract was superior to the standard drug albendazole (Raju et al., 2013).

41.3.9 CYTOTOXICITY

Many compounds of *S. violaceum* exhibited cytotoxic property against the Cancer cells (Yen et al., 2012). Compound 2 showed moderate activity against all disease cell lines (HepG2, Hep3B, A549, Ca9-22, MCF-7, and MDA-MB-231 with IC_{50} values of 2.22 ± 0.01, 2.95 ± 0.02, 3.09 ± 0.07, 2.95 ± 0.07, 4.78 ± 0.02, and 6.12 ± 0.15 μg/mL, respectively). Compound 8 showed moderate cytotoxicity against six cancer cell lines with IC_{50} values of 1.83–2.75 μg/mL. Compounds 3 and 9 showed the selective cytotoxicity against the Hep3B cancer cell line (3.32 ± 0.42 μg/mL and 2.87 ± 0.04 μg/mL, respectively), which is a p53 mutant cell line. Among the nonsteroidal saponins, compounds 12 and 13 exhibited feeble cytotoxic action with IC_{50} values of 8.18–17.53 μg/mL against four cancer cell lines (HepG2, Hep3B, A549, Ca9-22) (Yen et al., 2012).

41.3.10 WOUND HEALING ACTIVITY

Manjunatha (2006) unveiled the rate of wound healing property and provided the aqueous and ethanol extraction of the whole plant topically of *S. violaceum*. The injury-recuperating movement of watery and ethanol concentrates of leaf of *S. violaceum* was assessed utilizing extraction, entry point and dead space twisted models on rodents. For skin application, 5% w/w treatment of aqueous and ethanol extracts was ready in 2% sodium alginate and for oral organization suspensions containing 35 mg/mL and 20 mg/mL of watery and ethanol extract in 1% gum tragacanth were ready. The boundaries considered incorporates the pace of wound compression, time of epithelialization, skin breaking strength, granulation tissue breaking strength, dry granulation tissue weight, hydroxyproline assessment and histopathology of granulation tissue. The outcomes uncovered critical reduction in the time of epithelialization (18.22 ± 0.07 and 17.85 ± 0.04), huge expansion in skin-breaking strength (568.00 ± 3.11 and 589.17 ± 2.39), granulation tissue breaking strength (543.33 ± 2.12 and 567.53 ± 1.85), dry load of granulation tissue (53.89 ± 0.55 and 59.33 ± 0.54) and raised centralization of hydroxyproline in granulation tissue (1982.00 ± 0.58 and 2232.33 ± 0.76) in the creatures treated with aqueous and ethanol extract of *S. violaceum* separately, showing the power of both the plant extracts in advancing the injury mending process. Among the two extracts, the greatest movement was recorded in ethanol extract, contrasted with that of aqueous extracts. Notwithstanding, both the extracts were found to have critical injury recuperating advancing movement when contrasted and the control (Manjunath, 2006).

41.3.11 ANTIOBESITY AND ANTI-HYPERLIPIDEMIC ACTIVITY

The extract of *S. violaceum* was explored for absolute phenolic content (TPC), antiobesity, against hyperlipidemic, film security, and thrombolytic action. High-fat eating routine prompted corpulent mice to be utilized for antiobesity and antihyperlipidemic test. Complete phenolic content in root concentrate of *S. violaceum* was determined as 51.26 mg gallic acid comparable GAE/g of dry weight. The extractive supplementation with portions of 200 mg/kg and 400 mg/kg were fit for bringing down the degree of fatty substance and complete cholesterol essentially in high-fat eating routine (HFD) actuated corpulent mice in a portion subordinate way. As a layer settling specialist, rough concentrate had the

option to hinder the erythrocyte hemolysis fundamentally with a worth of 28.02 ± 5.09% and 32.97 ± 4.12% separately for heat and hypotonic arrangement initiated conditions. In addition, 21.56 ± 2.62% of clump lysis was shown by the extract for its thrombolytic action. Thus, the root of *S. violaceum* explains its potential as anti-obese agent (Ahamed et al., 2018).

41.3.12 HEPATOPROTECTIVE ACTIVITY

The ethyl acetate and chloroform extracts of *S. violaceum* were wealthy in phenolic and flavonoid substance individually. The DPPH and NO searching examine uncovered better action for ethyl acetate extract while ABTS test was better for the alcoholic extract. Further examinations on the hepatoprotective movement uncovered that the rebuilding of catalysts just as protein to ordinary levels after treating inebriated rodents with the bioactive concentrates in a dose-dependent manner. Likewise, histopathological concentrates on uncovered that the ethyl acetate extract was successful towards rebuilding of liver cells to typical levels. Accordingly, the phytochemical profile as assessed from the GC-MS investigation of the extract reduced the noticed reaction to four significant mixtures. The bioactive constituents, for example, viridiflorol, palmitic acid, n-pentacosanal, and citroflex A crediting to the noticed movement were uncovered by GC-MS investigation (Remya and Balamurali, 2020).

KEYWORDS

- **anti-obese agent**
- **chromatography**
- **gallic acid equivalent**
- **hepatoprotective activity**
- **pharmacology**
- ***Solanum violaceum***

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CHAPTER 42

Bioactive Compounds and Pharmacology of an Important Medicinal Plant: *Spilanthes acmella* Murr.

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42.1 INTRODUCTION

Spilanthes acmella Murr., belonging to the Asteraceae family, is a well-known documented endangered medicinal plant species with high potential to cure the problem of toothache (Nabi and Shrivastava, 2015). At the global level, it is native to Brazil and found distributed abundantly in tropical and subtropical regions. *S. acmella* is an annual, ornamental or medicinal herb that grows from 40 to 60 cm height in damp/marshy areas and can be cultivated throughout the year (Saraf and Dixit, 2002). Flowers and leaves of the plant have a pungent/bitter taste, which are used as folk medicine for stammering, toothache, stomatitis, and gums infection. This species of *Spilanthes* contains a wide array of bioactive compounds (like alkaloids, tannins, flavonoids, terpenoids, glycosides, phlobatannins, etc.), that are having multiple pharmacological properties such as antimicrobial, anti-pyretic, local anesthetic, insecticidal, larvicidal, antioxidative, aphrodisiac, analgesic, anti-diuretic, anti-inflammatory, and so on (Dubey et al., 2013;

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Prachayasittikul et al., 2013). The major fundamental phyto-constituent of this plant is 'spilanthol,' which is chemically an isobutylamide and responsible for resolving the problem of tooth ache and gum infection along with increased saliva secretion (Rani et al., 2019).

42.2 BIOACTIVE COMPOUNDS

A number of studies have been executed for chemical composition and structural analysis of bioactive compounds present in *S. acmella* (Ramsewak et al., 1999; Prachayasittikul et al., 2009). It has a diverse group of chemical constituents (Figure 42.1). The pharmacological properties of *S. acmella* are attributed to N-alkylamides chemical compounds, which are a category of bioactive constituents present in the genus *Spilanthes*. The major pungent constituent of N-alkylamide compounds in *S. acmella* is 'spilanthol' (N-isobutyl-2E, 6Z, 8E-decatrienamide), which is having natural insecticidal activities. Spilanthol was first time isolated from the flower head ethanol extract of *S. acmella* in 1945, which is found pungent in taste and traditionally used to cure tooth ache and stimulation of saliva secretion (Singh and Pradhan, 2015; Barbosa et al., 2016). Apart from this, many other chemical compounds have also been reported in *S. acmella* like triterpenoids, sesquiterpenoids, butylated hydroxytoluene and fatty acids (such as n-Hexadecanoic acid and tetradecanoic acid) from extracts of flower heads. The leaves of *S. acmella* are reported to contain alkaloids, carbohydrates, amide tannins, steroids, carotenoids, essential oil, amino acids, etc. (Savadi et al., 2010).

42.3 PHARMACOLOGY

42.3.1 ANTIBACTERIAL ACTIVITY

The antibacterial assay of different solvent extracts of *S. acmella* has shown excellent inhibitory response against both gram-positive and gram-negative bacteria. Previously, significant antibacterial activity of *S. acmella* extracts has been reported against pathogenic bacteria like *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Corynebacterium diphthiriae, Bacillus cereus, Escherichia coli, Klebsiella pneumoniae, Salmonella typhi*, etc. (Prachayasittikul et al., 2009; Arora et al., 2011; Thakur et al., 2019).

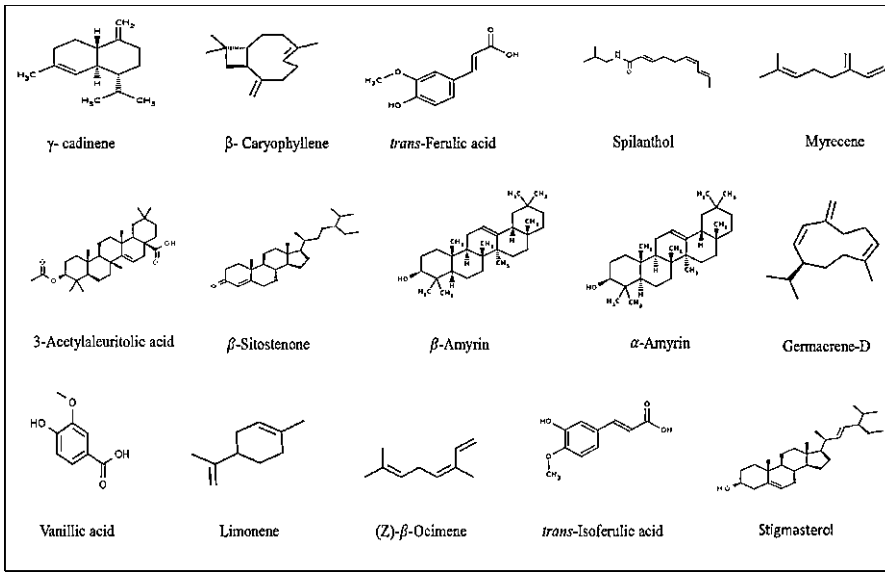


FIGURE 42.1 Chemical structure of bioactive compounds of *Spilanthes acmella* Murr.

42.3.2 ANTIFUNGAL ACTIVITY

In 2014, Khatoon et al. reported the antifungal potential of different plant parts like callus, stem, leaf, flower, etc., of *S. acmella* extracted with water and alcohol against *Candida albicans, Candida krusei, Aspergillus niger, A. flavus, A. fumigatus*, etc. However, aqueous extract was not found as much effective as alcoholic extract against all the tested fungal strains. The effect of different concentrations (0.1 to 2.0 mg) of *S. acmella* flower head extract on *Aspergillus niger, A. parasiticus, Fusarium oxysporum,* and *F. moniliforme* was also analyzed by Rani and Murty (2006). They found the diameter of inhibition zones ranged from 0.1 to 2.3 cm, against different fungal species.

42.3.3 NEUROPROTECTIVE ACTIVITY

In 2017, Suwanjang et al. investigated the neuroprotective effects of different solvent such as hexane, chloroform, ethyl acetate (EA), and methanol extracts of *S. acmella* against neuronal cells death induced by 24-hour treatment of pesticide (pirimicarb) and also elucidated the underlying molecular mechanism in dopaminergic human neuroblastoma (SH-SY5Y) cells lines. Results had revealed that *S. acmella* having a potential role in neuroprotection by the

regulation of calcium homeostasis with calpain and calpastatin, which may reduce cell degeneration in pirimicarb-induced neurotoxicity.

42.3.4 ANTIOXIDANT ACTIVITY

Antioxidant potential as free radical scavenging ability of *S. acmella* extracts have been previously estimated from different polar and nonpolar solvents (Rao et al., 2012). The ethanolic extract of *S. acmella* flower heads showed the highest anti-oxidative activity (using DPPH and ABTS assays) as compared to the other tested plant part extracts (Wu et al., 2008). However, Nanasombat and Teckchuen (2009) found weak antioxidant potential of methanolic extracts of *S. acmella* leaves and flowers. Prachayasittikul et al. (2009) reported that antioxidant activity of *S. acmella* could be due to the presence of phenolic and coumarin compounds in the plant extracts. They also showed the enhanced activity of super oxide dismutase (SOD) enzyme in the fractions isolated from chloroform extract of *S. acmella*, which might be due to the presence of bioactive molecules as triterpenoids, stigmasterol, and its glucosides. Tanwer et al. (2010) showed the antioxidant potential of methanolic extract of different *S. acmella* plant parts (stem, leaf, root, and callus) by using DPPH and superoxide radical scavenging assays. In DPPH assay, free radical scavenging activity was found maximum (76.42 ± 1.67%) in leaf methanolic extract. This study concluded that *S. acmella* possess a strong antioxidant activity as compared to the reference compound butyl hydroxytoluene (BHT).

42.3.5 ANTHELMINTIC ACTIVITY

Many studies have previously reported the anthelmintic activity of toothache plant (Singh et al., 2014; Lalthanpuii et al., 2020). Singh et al. (2014) have observed anthelminthic activity of aqueous extract of *S. acmella* callus against live trematode (fluke) parasites of cattle as the model test material. They revealed that aqueous and methanolic extracts exhibited varying degrees of activity at all tested concentrations with paralysis followed by death in tested parasites. These results also suggested that in-vitro cell cultures of *Spilanthes* can be a good substitute for effective natural anthelmintic drugs than field-grown plants.

Lalthanpuii et al. (2020) have performed a comparative study of anthelmintic potential between *S. acmella* plant extract and praziquantel (PZQ;

a prescribed anthelmintic medication used to treat infections of certain cestodes) against an intestinal cestode, *Raillietina echinobothrida*. This study was revealed that in terms of efficacy PZQ showed a good response towards cestode infection as compared to plant extract; however, *S acmella* extracts also showed moderate anthelmintic potential at all tested concentrations. *S. acmella* extract caused shrinkage and folds on the main body of cestode but not on the scolex region. These findings suggested that *S. acmella* is a good source of bioactive compounds having anthelmintic activity.

42.3.6 ANTI-INFLAMMATORY ACTIVITY

S. acmella anti-inflammatory property has been previously reported by many researchers (Chakraborty et al., 2004; Gupta et al., 2012; Prachayasittikul et al., 2013). Wu et al. (2008) demonstrated that spilanthol exert anti-inflammatory action *via* inhibition of NF-κB pathway, afforded reduction in mRNA level and protein expression of COX-2 and inducible nitric oxide synthase (iNOS). The anti-inflammatory activity of *S. acmella* can be attributed to inhibition of COX and LOX owing to the similar structures of the main compound of plant spilanthol and arachidonic acid. Moreover, ethanol extract of *S. acmella* leaves exhibited significant anti-inflammatory activity against acute (carrageenan induced rat paw edema method), subacute (granuloma pouch method) and chronic (adjuvant arthritis method) inflammation (Barman et al., 2009).

42.3.7 LARVICIDAL ACTIVITY

Saraf and Dixit (2002) analyzed the larvicidal activity of spilanthol against the eggs, various instar larvae and pupae of the *Anopheles*, *Culex*, and *Aedes* mosquito species. They reported about larvicidal potential of *S. acmella* flower heads alcoholic extract with 100% mortality rate of eggs, larvae, and pupae (at maximum 7.5 ppm concentration) due to the presence of spilanthol. They also found spilanthol high mortality against eggs and pupae at low doses. This study has revealed that *S. acmella* extract worked on the nervous system of pupae and showed abnormal symptoms as jerks, spinning, and uncoordinated muscular activity. The mortality of pupae in a short span of time also indicated that spilanthol mainly disrupted the ongoing processes of histolysis and histogenesis. Similarly, Pandey et al. (2011) also observed the bio-larvicidal potential of micropropagated plants of *S. acmella* against late III/early IV instar *Anopheles stephensi* larvae.

42.3.8 APHRODISIAC ACTIVITY

In 2011, Sharma et al. observed the aphrodisiac effect of *S. acmella* plant extract in male rats. They analyzed increased mount latency, intromission latency, ejaculation frequency, and postejaculatory interval in a dose-dependent manner after oral administration of plant extract. They also reported that these benefits were more significant after 28 days of supplementation relative to 14 days and *S. acmella* had more superior aphrodisiac potential compared to Viagra in all aspects studied except proerectile properties.

42.3.9 LOCAL ANESTHETIC AND ANTIPYRETIC ACTIVITY

The anesthetic activity of *S. acmella* has been analyzed by using two different animal model namely: (i) intracutaneous application in guinea pigs using nupercaine as standard; and (ii) plexus anesthesia in frog using cocaine as standard (Chakraborthy et al., 2002). The response of local anesthetic action was very potent, which could be due to the presence of alkylamides.

In 2010, Chakraborty et al. studied the antipyretic activity of *S. acmella* by yeast induced method. This study has suggested that the antipyretic activity of this plant could be due to the presence of high content of flavonoids that act as a predominant inhibitor of cyclooxygenase/lipo-oxygenase.

42.3.10 DIURETIC ACTIVITY

S. acmella plant extracts have been investigated for diuretic property (Ratnasooriya et al., 2004; Kumar et al., 2010). Previous studies have revealed that *S. acmella* ethanol extracts have diuretic activity, which might be due to the presence of tannin, steroid, alkaloids, and carotenoid (Vanamala et al., 2012; Yadav et al., 2011). Ratnasooriya et al. (2004) suggested that *S. acmella* extract acted as a loop diuretic, which is the most powerful among all diuretics.

42.3.11 HEPATOPROTECTIVE ACTIVITY

Shah et al. (2018) reported the hepatoprotective activity of methanolic extract of *S. acmella* aerial parts against paracetamol-induced liver damage. They evaluated that the paracetamol significantly increased the levels of alanine

transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) as compared to control, while plant extract (400 mg/kg) reversed the elevation in the level of ALP, AST, and ALT caused by the hepatotoxicants.

42.3.12 IMMUNOMODULATORY POTENTIAL

S. acmella leaves ethanolic extract showed significant activation of macrophages and suggested the immunomodulatory activity of the plant as a potential natural drug for immune stimulant effect (Yadav et al., 2011). The assessment of immunomodulatory potential was carried out by testing the humoral (antibody titer) and cellular (foot pad swelling) immune responses to the antigenic challenges with sheep RBC and by neutrophil adhesion test. Rajesh et al. (2011) found that orally administered plant extract showed a significant increase in neutrophil adhesion, hemagglutinating antibody titer and delayed-type hypersensitivity (DTH) responses. Savadi et al. (2010) also evaluated the immunomodulatory potential of *S. acmella* ethanolic extract using different experimental models like modulation of macrophage function (morphometric and functional changes in mice), carbon clearance assay with the help of Indian ink dispersion in mice and immunoprophylactic effect with the help of *E. coli* in mice. This immunomodulatory activity was accompanied by less nitric oxide (NO) synthase and cyclooxygenase-2 mRNA content, less cytokine production, and less nF-kB activation.

42.3.13 ANTICANCER ACTIVITY

In 2008, Wu et al. had demonstrated the anticancer activity of spilanthol, which is the major phytoconstituent of *S. acmella*. Spilanthol inhibited NO production in a murine macrophage cell line model, RAW 264.7 along with down regulation of inflammatory mediators interleukin (IL)-1â, IL-6 and tumor necrosis factor (TNF-á) related gene expression. This study has suggested that spilanthol can be a used as an important inflammatory mediator's inhibitor in the near future. Similarly, Lalthanpuii and Lalchhandama (2019) also analyzed the anticancer potential of *S. acmella*. They have used Dalton's lymphoma ascites (DLA) and chinese hamster lung carcinoma (V79) cell lines for anticancer assays and concluded that the plant extract showed anticancer activity on lymphoma cells. Boontha et al. (2020) reported the anticancer activity of *S. acmella* ethanolic extract against the breast cancer cell line MCF-7 with IC_{50} value of 37.1 ± 1.1 μg/mL in 48 h. Therefore, this

plant species can be further adopted as a promising source for anticancer drug development in the upcoming time.

42.3.14 PANCREATIC LIPASE INHIBITION ACTIVITY

Ekanem et al. (2007) have reported *S. acmella* pancreatic lipase inhibitory activity. They observed that 70% ethanolic extract of *S. acmella* flower bud can significantly inhibit human pancreatic lipase in a concentration-related manner in *in-vitro* conditions.

42.3.15 ANTI-MALARIAL ACTIVITY

S. acmella is a well-known folk medicine for the treatment of malaria in Africa and India (Spelman et al., 2011). A previous study of Mbeunkui et al. (2011) showed that spilanthol and acetylenic alkamide (undeca-2E-ene-8,10-diynoic acid isobutylamide or UDA) isolated from the root ethanolic extract of *S. acmella*, worked as an antimalarial agent against two different strains of *Plasmodium falciparum* (known as PFB strain and K1 strain originated from Brazil and Thailand, respectively). As well as, *in-vitro* regenerated *S. acmella* root's hexane extract also exhibited 100% larvicidal activity against malaria and filarial vectors (Pandey and Agrawal, 2009). In addition, Bae et al. (2010) also demonstrated the antimalarial activity of *S. acmella* plant and suggested their importance towards the prevention of malaria in the future as an herbal drug.

KEYWORDS

- **anthelmintic activity**
- **anticancer activity**
- **antimalarial agent**
- **aspartate transaminase**
- **butyl hydroxy toluene**
- ***Spilanthes acmella***
- **spilanthol**

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CHAPTER 43

Pineapple [*Ananas comosus* (L.) Merr.]: A Biological and Pharmacological Active Medicinal Plant

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43.1 INTRODUCTION

Ananas comosus (L.) Merr. **(**Pineapple) is a common tropical plant, the third most essential tropical fruit crop. Pineapple belongs to the family Bromeliaceae. It is mostly grown in the tropics and subtropics with optimum production from Thailand, the Philippines, Brazil, China, and India. It is a commercial crop with great economic, industrial, and pharmacological importance in many parts of the world (Hossain et al., 2015).

Pineapples are not only commercially important but are also important nutritionally beneficial plants (Ancos et al., 2016). Researchers have documented the nutritional and possible health benefits of pineapple diets. Some of the beneficial and health-related benefits of pineapple that have been reported include antibacterial activities, antioxidant effects, antiviral activities and antifungal effect (dos Anjos et al., 2016; Ivanova et al., 2019; Taira et al., 2005).

43.2 BIOACTIVE AND PHARMACOLOGICAL PROPERTIES OF *ANANAS COMOSUS*

Pineapple has been described in ethnobotanical literature to possess highly effective pharmaceutical compounds. Although all the active ingredients responsible for the identified pharmaceutical activities of pineapple have been given attention, one important ingredient that has been identified is bromelain (Figure 43.1). The chemical structure of bromelain has not been fully determined, but it is presumed to have a configuration that may include some peroxidases, protease inhibitors, acid phosphatase, and a bond to calcium. Bromelain is known to function as a proteolytic enzyme, acts as an immune modulator or a hormone signaling pathways intracellularly. Experimentally, bromelain has been shown to inhibit or induce T cells production of the Th cytokines IL-4, and to a lesser 2° the Th cytokines IL-2. It also induces interferon-1 gamma (IFN) by modulating the extracellular regulated kinase-2 (ERK-2) through intracellular signaling protection techniques (Mynott et al., 1999) as reported by Tochi et al. (2008). In other studies, bromelain actively reduce the CD4 + T-lymphocytes count in animal model and in turn inhibit inflammation (Manhart et al., 2002). Other pharmacological activities of bromelain has been reported to include anti-tumor activities, inhibition of thrombus formation, healing of burnt wounds and tissues (Tochi et al., 2008).

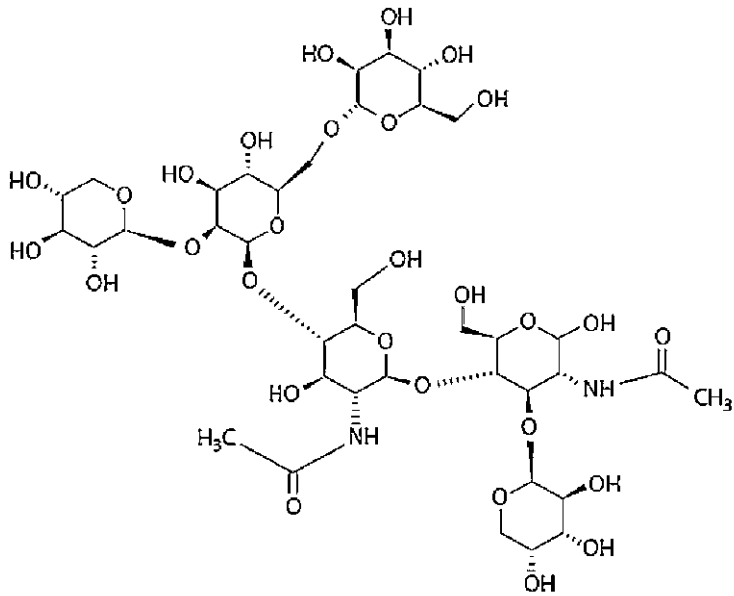


FIGURE 43.1 The chemical structure of bromelain.

Ananas comosus (Pineapple) is a well-known plant that is edible and has various nutritive compositions, including vitamin C, sugar, and a proteolytic enzyme known as bromelain, which is responsible for protein breakdown. It also has the unique quality of having high potassium and low content of sodium (US NIH, 2020). Bromelain also has the potential of causing injury and cell death due to its ability to induce protein breakdown in the bacterial membrane, while saponin in *A. comosus* worked by increasing the permeability of the membrane of a bacterial cell. Its action involves quick cell penetration that influences, cell metabolism and denatures proteins on the cell membrane, causing membrane lysis. Previous research expressed that antioxidant activity may be related to anthocyanins, catechins, isoflavones, flavones, and other phenolics compounds inherent in the pineapple (Mhatre et al., 2009).

There are different kinds of compounds found in the crude extract of the plant out of which the most studied is the cysteine proteinases. Researchers are of the opinion that the enzyme is responsible for the unique health benefits that are known in bromelain. There are other documented studies that reported the vital health benefits of bromelain which are associated with innate bioactive constituents in the extract. The chemically active extract could be obtained from the stem or fruits of *A. comosus*. Basically, the fruit and the stem marginally vary in the chemical compositions of extracts,

although the inherent prospect underlying practical usefulness created by the differences remains unclear even though there are more studies that used the extract from the stem.

A. comosus is rich in vitamin C which is a potent water soluble antioxidant that helps in defending the human body from free radicals and mitigating oxidative stresses. Vitamin C also plays a critical role in the optimal functioning of the human immune system, boosting resistance against ear infection, flu, and cold (Date et al., 2016). *A. comosus* is a vital source of mineral elements such as manganese, which is a useful cofactor for the functioning of various metabolic enzymes relevant in the energy production and human defenses. It also assists superoxide dismutase in disarming free radicals produced in the mitochondria. A cup of the freshly prepared juice from *A. comosus* provides an appreciable amount of this mineral nutrient. *A. comosus* is a remarkable source of vitamin B, which is also a very useful cofactor (Monji et al., 2015).

Analysis of *A. comosus* juice secondary metabolites revealed the presence of compounds such as ethyl acetate (EA), iso butyrate, acetaldehyde, isopropyl, N-propyl formate and histidine (Lawal, 2013). Similarly, ethyl, and methyl esters, alanine, dimethy, ethyl caproate, caproic acid, acetoxycaproic, and ferulic acid are also associated with pineapple (Kataki, 2020). The leaves of *A. comosus* contain compounds like methionine, glycine, argentine, phenylalanine, tyrosine, and allylhexanoate (Monji et al., 2018). In a study, Arshad et al. (2017) reported the presence of huamol, and haumine which are indole alkaloids as well as hemicelluloses in *A. comosus* fruit. Furthermore, the presence of enzymes such as papain has been documented as present in the stem and other compounds such as alkaloids have also been reported along with cinnamic acids and coumaric which belong to the group known as phenylpropaniods (Monji et al., 2015; Lawal, 2013).

In a related study, bromelain was isolated from the peel of unripe pineapple fruit by Monji (2016). Various volatile organic compounds like ethyl and methyl esters of octenoic acid, nonanoic acid, and oct-trans-enoic acids have also been isolated and characterized from the fruit. The presence of sulfur-based compounds such as methyl mercaptan was reported (Huang et al., 2015) while butanol, its derivatives which are basically essential (Kargutkar and Brijesh, 2016) and a novel steroidal strihydroxtriterpene carboxylic acid (stem) were equally reported (Takata, 1976). Kargutkar and Brijesh (2016) obtained flavonoids from pineapple leaves. In another work, Lawal et al. (2013) documented various phytochemicals such as saponins, alkaloikds, tannins, phytosterols, and triterpenoids from the ethanol plant extract.

Riya et al. (2014), in a related work, documented the presence of steroids and triterpenoids in the leaf extract of *A. comosus* using petroleum ether (PE) as extractant; other compounds, such as steroids and alkaloids were found in the chloroform extract while glycosides, steroid, and saponins were present in the methanol extract. It has been observed that naturally occurring substances have inhibitory activity against bacteria present in plants; hence they are employed in alternative medicine practices. This is attributed particularly to the natural presence of active ingredients, such as flavonoids which ruptures bacterial cells and inhibits their enzyme activities (Zharfan et al., 2017).

Ananas comosus fruit has numerous bioactive compounds like flavonoids, vitamin C, phenolic compounds, and β-carotene, with commercial benefits (Figure 43.2).

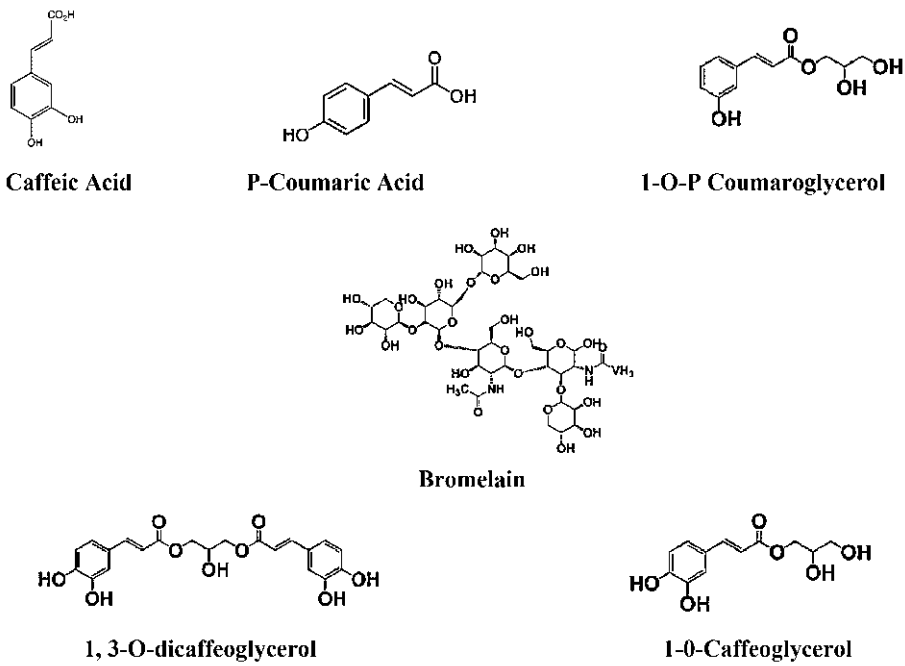


FIGURE 43.2 Schematic illustrations of bioactive components of pineapple plant.

Awanis et al. (2020) used metabolomics schemes to assay some of the bioactive metabolites and their diversity by means of diverse solvent ratios. The extract obtained from *Ananas comosus* wastes was tested for

total phenolic content, nitric oxide (NO), and free radical scavengers using DPPH along with α-glucosidase inhibitory activities. In addition, the highest total phenolic content was established throughout the samples, which was extracted by means of a 50% ethanol ratio. However, it was noted that extraction using absolute ethanol yielded the maximum inhibition for α-glucosidase activity of the peel at IC_{50} value of 92.95 g/mL. The data analyzes were carried out using ^{1}H NMR treated with analysis multivariate data. Some of the compounds analyzed were threonine, 3-methylglutaric acid, valine, syringic acid, α-linolenic acid, and catechin (Figure 43.3).

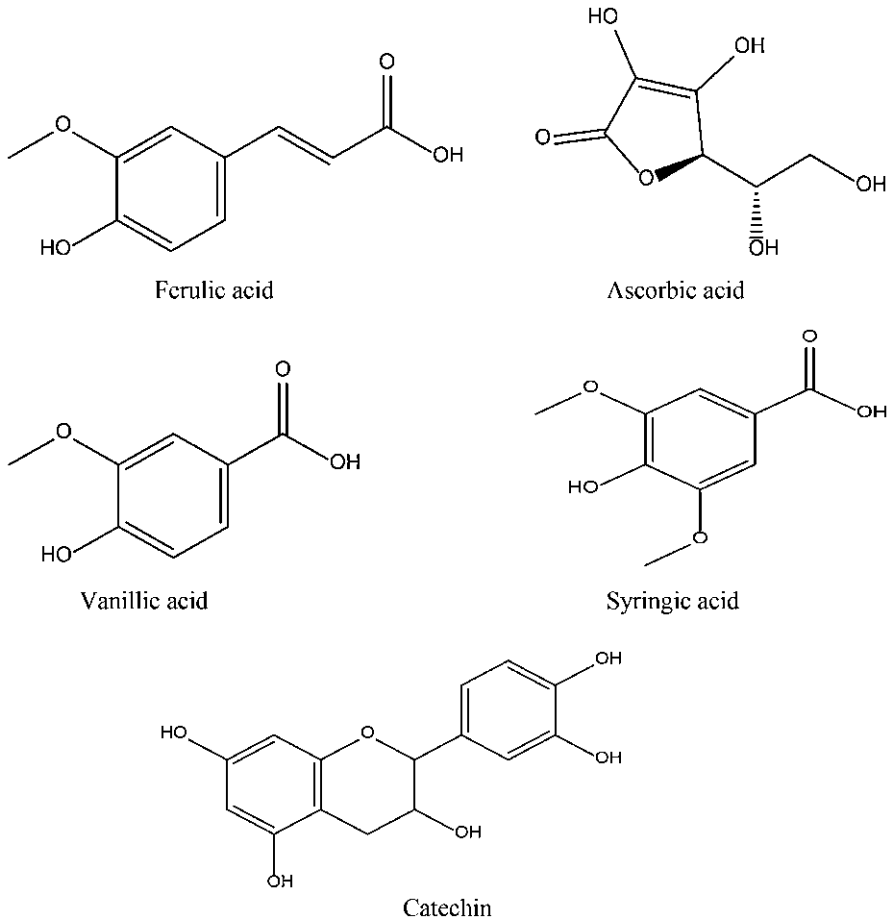


FIGURE 43.3 Chemical representations of compounds assayed from *Ananas comosus* plant.

43.3 PHARMACOLOGY

Hartati and Suarantika (2020) reported that diverse portions of *Ananas comosus* are utilized in traditional medicine. Certain parts of the plant are used as anti-edema, anti-inflammatory agent, antimicrobial, purgative, vermicide, and for the treatment of digestive disorders. Some compounds were obtained from the phytochemical constituents of *A. comosus* that have been implicated in traditional medicine and they include quercetin, ascorbic acid, flavones, flavones-3-ol as well as ferulic acid. The anti-inflammatory, antifungal, antibacterial, and antioxidant were identified as pharmacotherapeutic drugs from the crude extracts of *A. comosus*.

Moreover, Lawal (2013) opined that several parts of *Ananas comosus* have been reported to consist of proteolytic, anti-inflammatory, and antihelminthic agents. Similarly, the plant has received attention as therapeutics for indigestion, diarrhea, bronchitis, pneumonia, pain, arthritis, diuretic, heart disease, abortion, venereal diseases, hemorrhoids, edema, emmenagogue, purgative as well as vermifuge. The plant was described to comprise of flavonoids, alkaloids, tannins, saponins, triterpenoids, steroids, and phytosterols.

43.3.1 ANTIBACTERIAL ACTIVITIES

Extracts from pineapple have been used to control microorganisms and helminths (dos Anjos et al., 2016). The compound from pineapple with antimicrobial effect is bromelain. Bromelain has been applied in the management of *Alicyclobacillus* spp., a commensal which is known to cause foul odor in citrus. In a related study, pineapple extract was tested against two oral pathogens (*Streptococcus mutans* and *Enterococcus faecalis*) (Ahamed et al., 2016). The extract showed effective inhibition of this pathogen at different concentrations (Ahamed et al., 2016b). Extracts from different parts of pineapple have been used for *in vitro* study against many microbes. Kabir et al. (2017) demonstrated the efficacy of alcohol extract of pineapple on some pathogenic bacteria such as *Klebsiella*, enterotoxigenic *E. coli* (ETEC), *Enterobacter cloacae*, *Shigella flexneri*, *Staphylococcus aureus*, *Enterococcus faecalis*, enteroaggregative *E. coli* (EAEC), and *Pseudomonas aeruginosa*. Bromelain isolated from pineapple proved to be a promising antibacterial agent that is efficacious at room temperature (37°C) against *Proteus* spp. and *E. coli*, respectively. Juice from pineapple has also been used in the management of infections, pain, muscle soreness, etc. (Bansode

and Chavan, 2013). The antibacterial activities of bromelain is associated with its disruption of the signaling pathways. For example, if the target is an intestinal pathogen, bromelain is reported to block its interaction with the intestinal signal pathways which include guanosine 3′:5′-cyclic monophosphatase (cGMP), adenosine 3′:5′-cyclic monophosphatase (cAMP), and calcium-dependent signaling cascades (Praveen et al., 2014). The antiadhesion property of bromelain is also vital to its action in the control of bacteria.

The leaves extract obtained from *A. comosus* has an inhibitory concentration (MIC) ranging from 1.65 to 4.95 mg/ml against various groups of microbes such as *Bacillus subtilis, Candida albicans* and *Staphylococcus aureus* (Praveen et al., 2014). On the basis of previous study, it is reported that saponin and bromelain were vital components in the sensitivity of gram negative bacteria, whereas polyphenols and flavonoids showed potency in the inhibition of the gram-positive bacteria by rupturing the peptidoglycan layer.

Various groups of microbes that are multidrug resistant such as *P. aeruginosa,* were eliminated by the extract at 0.2 mg/ml. It also has a bacteriocidal effect on *S. pneumoniae* and *S. aureus*. However, it was reported from another study that the plant peel methanol extract was inactive against *B. subtilis*, and *E. coli* at 50 mg/ml, but showed activity at a 100 mg/ml on *S. typhi* (Ishii et al., 1984).

Teai et al. (2011) reported that the chloloform extract of the peels of *A. comosus* had activity against *Corynebacterium rubrum* with a zone of inhibition of 9 mm, *Staphylococcus aureus* having 11 mm zone of inhibition, *S. typhimurium* with a zone of inhibition of 9.3 mm and *Enterobacteria aerogenes* with 9.33 mm inhibition zone. The extract of the *A. comusus* peel prepared using n-hexane as solvent showed effectiveness against *S. typhimurium* and *S. subflava* but not active against *S. mirabilis*, *K. pneumoniae* and *S. aerogenes* (Xie et al., 2017).

In a related work Taura et al. (2005) documented that the plant ethanol extract showed a remarkable *in vitro* activity against *S. typhi* at a dose of 100 mg/cm^3, with 15 mm zone of inhibition in the diameter and minimum inhibitory concentration of 80 mg/cm^3. Lawal et al. (2013) showed that *A. comosus* peel ethanol extract had antibacterial activity on *A. hydrophilia* and *Salmonera* species. Previous research affirmed that the combination of bromelain and antibiotic therapy was more effective in the treatment of cutaneous *Staphylococcus* infection, pneumonia, bronchitis, thrombophlebitis, pyelonephritis, cellulitis in perirectal and rectal abscesses, urinary tract infections and sinusitis (Gaspani et al., 2002; Rathnavelu et al., 2016).

A combined therapy using ox bile, bromelain, and pancreatin were found to be efficient in the reduction of fat excretion in patients with pancreatic steatorrhea, pains, frequency of defecation and flatulence (Pellicano et al., 2009). Also, trypsin, bromelain, antibiotics, and rutin have been combined and administered as adjuvant therapy in children that have sepsis.

The pineapple extract antibacterial potential at various concentrations screened by agar well diffusion technique showed that the extract was inhibitory of *E. coli* showing 26 mm in diameter as the zone of inhibition at 1,000 µg/ml. The activity for *P. aeruginosa, K. pneumoniae* and *S. aureus* were reported to be 20 mm, 22 mm and 23 mm, respectively (Zharfan et al., 2017). The sensitivity of *S. mutans* at 2 mg/ml is similar in comparison with *E. fecalis* at 31.25 mg/ml.

Praveen et al. (2014) reported that bromelain has an antibacterial potential against periodontal pathogens and hence could be employed for antibacterial purpose (Praveen et al., 2014). Similarly, Vuyyuru et al. (2020) documented that the extracts from the plant showed high potency and remarkable antioxidant activity and a moderate potency against bacteria and four typical food borne microbes.

Antimicrobial sensitivity was observed by Namrata et al. (2017) in ethanolic extract with an inhibition zone diameter of 15 mm, 14 mm, 14 mm and 21 mm against *Bacillus amyloliquifaciens, Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli*, respectively.

43.3.2 ANTIVIRAL ACTIVITIES OF PINEAPPLE

The antiviral properties of pineapple was first mentioned in 1978 by Konowalchuk and Speirs when they tested the antiviral properties of commercial beverages in Canada (Konowalchuk and Speirs, 1978). In this study, there were no evidence-based report on the antiviral activities of Pineapple suggesting dearth of information on it antiviral activity even in recent time. Hossain et al. (2011) reported the therapeutic potential of *A. cosmosus* juice against polio virus.

43.3.3 ANTIFUNGAL ACTIVITIES OF PINEAPPLE

There was a documented report on the activity of the extract from the peels against *Candida albicans, C. tropicalis, C. glabrata* and *Crytococcus luteolus* (Chanda et al., 2010). The acetone extract of the pineapple peels showed

high activity against *C. rubrum* giving 9 mm inhibition zone, *C. albicans* with 10.5 mm inhibition zone. The extract from the peel using methanol did not show activity against *C. rubrum* (Kalaiselvi et al., 2012).

The pineapple bromelain ability to inhibit fungi was demonstrated in many studies, Lopez-Garcia et al. (2012) used bromelain to inhibit fungal pathogens in plant. Their study showed inhibition of the fungal pathogen due to the protease activities (López-García et al., 2012). Similarly, Taira et al. (2005) purified a chitinase enzyme from pineapple which exhibited a very good activity against *Trichoderma viride* (Taira et al., 2005).

The *A. comosus* chloroform and acetone extract had antimicrobial activity against *Candida albicans, Candida glabrata, Cryptococcus luteolus, Candida tropicalis*, and *Candida rubrum* (Ajibade et al., 2015). In the findings of Dabesor et al. (2017) the antimicrobial activities corresponded with the phytochemical constituents of ethanol and aqueous extracts of *Ananas comosus* peel on particular food-borne pathogens. The *A. comosus* peel ethanol extract showed sensitivity zone against *E. coli, B. cereus* as well as *S. aureus* with 12.3.0 ± 0.12 mm, 14.0 ± 0.22 mm and 15.0 ± 0.6 mm zone values, respectively. Also, analysis of phytochemical constituents disclosed the presence of alkaloids, oxalate, tannins, phytate along with glycoside. In conclusion, pineapple is rich in the enzyme bromelain and phytochemicals, which play significant role in maintaining healthy living and should be considered as a nutraceutical for the ameliorating different ailments.

43.3.4 ANTIPYRETIC EFFECTS

Vijayanand and Sanjana (2017) corroborated the application of various parts of *Ananas comosus* for the management of inflammation, headaches, pains, and pyretic. Lawal (2013) reported that *Ananas comosus* contains high amount of alkaloids, saponins, flavonoids, tannins, triterpenoids, phytosterols, and steroids which boost its use as antiparasitic and analgesic agent. Consequently, the consumption of *A. comosus* extract can boost the immune system and hydrate the body against fever (Prasenjit et al., 2012). In addition, bioactive molecules such as vitamin A, β-carotene, vitamin C, bromelain, folates, flavonoids, thiamin, riboflavin, pyridoxine, pectin, and minerals occur in *Ananas comosus* extract. These biomolecules have shown great potential against *Salmonella typhi*, suggesting why the plant extract has attracted interest as an antipyretic agent and potent treatment against Typhoid fever.

43.3.5 CARDIOVASCULAR AND CARDIOPROTECTIVE EFFECTS

Vijayanand and Sanjana (2017) associated the high level of flavonoids and phenols like vitamin C, terpenoids, saponins, flavonoids, tannins, β-carotene, anthraquinones, alkaloids, resins, carbohydrate, phenols like gallic acid, vanillic acid, epicatechin, and catechin, steroids, oil with strong antioxidant capacities for cardioprotective, anti-atherosclerotic, and anti-hypercholesterolemia effect of phenolic extract of *Ananas comosus* with its ethnobotanical applications. These active ingredients are known to prevent cardiac complications, hypoglycemic, and antidiabetic properties.

Saksri and Kumpun (2019) also linked the beneficial role of *Ananas comosus* fruit assay utilizing hexane, methanol, and dichloromethane to its antioxidant capacity against free radicals after carrying out 2,2-diphenyl-1-picrylhydrazyl assay. This led them to promote *Ananas comosus* as a viable material for pharmaceutical product development and functional food for the prevention of various cardiovascular diseases such as blood coagulation, tumor, and inflammation.

Manzoor et al. (2016) confirmed that the active constituent in *Ananas comosus* is bromelain. Bromelain has diverse physiological functions, act as a proteolytic enzyme and phytomedicine. It also acts in the blockage of platelet aggregation, as anti-thrombotic, anti-edematous, anti-inflammatory, and regulates immunity by the reduction in the level of CD4+, bradykinin, T lymphocytes and modulation of cytokines. This affords it the potential for tremendous circulatory improvement and cardiovascular properties. Also, *Ananas comosus* has huge amount of proteinases and several thiol endopeptidases like comosain, cysteine, ananain, peroxidases, acid phosphatase, in addition to high amount of protease inhibitors like cellulases, glucosidases, glycoproteins, organically intact Ca^{2+} and carbohydrates. Some of these compounds are known to display great cardioprotective functions such as anti-edematous, anticancer, fibrinolytic, anti-inflammatory, anti-coagulative, antithrombotic, antibiotic, and reduction in cell receptors like plasma fibrinogen and hyaluronan receptor CD44 levels.

Also, bromelain act as inhibitor of thrombosis, blood viscosity, risk of thrombophlebitis, and lowers clumping of platelets as well as decrease the severity of angina pectoris. Bromelain acts as a fibrinolytic agent by increasing the conversion of plasminogen to plasma and subsequently inhibiting fibrin. There is also reduction in fibrinogen ration in the serum, reduces prekallikrein, decline in platelet aggregation by ADP induction and delay

the activated partial thromboplastin and prothrombin time, thus facilitating increased circulatory function.

Yuris and Siow (2014) identified three varieties of *Ananas comosus* such as Josephine, Morris, and Sarawak which have abundant amount of antioxidant activity and biomolecules such as ascorbic acid and polyphenols like p-coumaric acid, quercetin, flavones, flavones-3-ol, tannic acid, caffeic acid, ferulic acid, and catechin which significantly contribute to the antioxidant property as well as assisted in reducing the morbidity of cardiovascular disease. Pavan et al. (2012) linked *Ananas comosus* thiol endopeptidases, glucosidase, phosphatase, peroxidase, escharase, protease inhibitors and cellulose which are the active constituents to its fibrinolytic, antithrombotic, anti-inflammatory, and antiedematous activities. Also, they associated bromelain with the mediation of angina pectoris, sinusitis, bronchitis, surgical trauma, thrombophlebitis, osteoarthritis, different cardiovascular disorders.

Kargutkar and Brijesh (2016) affirmed that *Ananas comosus* contains ananasate, chlorogenic acid, beta-sitosterol, rutin, bromelain, naringenin, flavonoids, glycosides, serotonin, adrenaline, dopamine, non-adrenaline, tannins, triterpenoids, and phytosterols which confers the ability to protect against different oxidative stress mechanisms. Based on their study, bromelain exerts antihypertensive effects, breakdown of cholesterol plaques, increase the membrane permeability to oxygen and other important nutrients, increases blood fluidity, dissolution of arteriosclerotic plaque, and potent fibrinolytic activity (Vidhya et al., 2016).

Further study showed that *A. comosus* has great antioxidant activity due to the presence of bromelain thus, capable of maintaining cell membrane integrity, improving cardiac systolic/diastolic dysfunction, reducing myocardial damage, and suppressing oxidative stress (Saxena and Panjwani, 2014). Dysfunctional blood circulation and heart are two challenges of cardiovascular disease. The coronary and carotid arteries are greatly affected by this increasing the risk of heart attack and premature death. The consumption of *Ananas comosus* was shown by Hamadou et al. (2017) to significantly decrease total cholesterol rates, low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and glucose linked with regular aerobic exercise. Many studies also affirmed that consumption of polyphenol-rich food offer protective role against several diseases especially the cardiometabolic disorders. These polyphenol-rich compounds, have the capacity to mop up free radicals, decrease oxidative stress, prevent oxidation of biomolecules. *Ananas comosus* has been identified as a good source of polyphenol rich biomolecules (Putri et al., 2018; Ali et al., 2020).

Das et al. (2019) highlighted the importance and effectiveness of *Ananas comosus* silver nanoparticle (AC-AgNPs) in the treatment of acute illnesses, drug formulation and several other diseases like cardiometabolic, diabetes, and bacterial infections. The authors showed that AC-AgNPs action could be attributed to functional groups on the polyphenolic surface. The biomolecules have displayed great beneficial potentials in the immune, nervous, and cardiovascular system. AC-AgNPs act against NO, which is the main bio-regulatory molecule in the control of several physiological function, and prevention of numerous diseases like cancers, arthritis, inflammation, cardiometabolic dysfunction. The mechanism of pathophysiology of NO involves its reactivity, becoming more sensitive when combined with singlet oxygen to form highly reactive biomolecules that can generate numerous cellular aliments such as fragmentation of cellular, peroxidation of lipids and prevention of nitrite formation, through stabilization and capping of AC-AgNPs.

Dutta and Bhattacharyya (2013) noted the cardio protective benefit of *A. comosus* extracts. The aqueous and ethanol extracts of various parts of the plant were observed to reduce the cholesterol, triglycerides, alanine transaminase (ALT), and partate transaminase contents in the body as well as an increase in the level of HDL. The *in vivo* and *in vitro* experiment revealed the potential of bromelain at reducing the severity of transient ischemic occurrences; angina pectoris and also aiding the prevention of coagulation of human platelets thereby mitigating the symptoms of high blood pressure among humans. Yabesh et al. (2014) in a related study affirmed the ability of bromelain to reduce the damage due to apoptosis and endothelial cell in the occurrence of hepatic ischemia. It was capable of dissolving arteriosclerotic plaque in the model organism through the breakdown of cholesterol plaques. There was also documented antioxidant activity.

43.3.6 HEPATOPROTECTIVE AND ANTI-ULCER EFFECTS

After four weeks of treatment, Yantih et al. (2017) documented that pineapple juice caused a drop in aspartate transaminase, ALT in isoniazid exposed rats. Administration of ethanol extract of pineapple at 200 $mgkg^{-1}$ and 400 $mgkg^{-1}$ body weight elicited a fall in glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, total protein, total bilirubin in rats exposed to paracetamol in the serum. In doliprane poisoned rats, pineapple extract at 0.06–0.12 mg/kg body weight orchestrated an attenuation in hepatic

lesion. With respect with the anti-ulcer of *Ananas comosus*, Sowjanya et al. (2016) reported that 100 mg/kg and 200 mg/kg body weight of peel extract improved ulcer healing. Ethanolic extract of ripe pineapple fruits exerted the protective effect on ulcer healing in dose dependent manner (Mallik et al., 2019). *Ananas comosus* extract treatment was shown to reduce hepatotoxicity orchestrated by paracetamol exposure (Dougnon et al., 2009).

43.3.7 NERVOUS EFFECTS

Helen et al. (2019) noted that the secondary metabolites inherent in *Ananas comosus* extract act pharmacologically against some neurological dysfunctions such as Alzheimer's disorder, Parkinson, and reperfusion abnormalities. This is due to its antioxidant and anti-inflammatory effects that slow down the reaction produced by oxidants, thus stabilizing and reducing their damaging effects. Kafeel et al. (2016) attributed the antidepressant potentials of *Ananas comosus* extract to the richness in neurotransmitters like serotonin, dopamine, and nor epinephrine, Moreso, neuropsychiatric conditions such as anxiety or depression are described by lack of Norepinephrine and Serotonin which generally lead to brain disorder, emotional trauma, declined abilities or routine cognitive activities. The pathophysiology of depression is the lack of essential neurotransmitters in the brain like serotonin, dopamine, norepinephrine, elevated lipid peroxidation (LPO) level, low antioxidant activity in the central nervous system (CNS) all of which are potentially amenable by *Ananas comosus.*

Kafeel et al. (2016) reported the remarkable role the phytochemical constituent of pineapple on the CNS. Again, the rich antioxidant content like the polyphenols like myricetin, tannic acid, salicylic acid, chlorogenic acid, p-coumaric acid, rutin, quercitrin, naringenin, trans-cinnamic acid, kaempferol, and others like saponins have shown antidepressant and anxiolytic bioactivities. This was suggested to be due to its ability to alter the serotonergic pathways and the catecholamine conduction. Li et al. (2014) reported that *Ananas comosus* extract consist of gallic acid, catechin, epicatechin, ferulic acid with huge antioxidant capacity. Ali et al. (2020) revealed that the thiamine content in *Ananas comosus* extract is essential for maintaining the nervous system functions. Thiamine is particularly good in decreasing metabolic alterations as a result of diabetes and glucose that may have a negative effect on the nervous system.

43.3.8 ANTI-INFLAMMATORY EFFECTS

Inflammation is critical in the pathogenesis of diseases. Therefore, its reduction could reduce the disease incidence and severity drastically. The anti-inflammatory potentials of *A. comosus* is linked to bromelain whose activity is comparable to nonsteroidal anti-inflammatory drugs (NSAIDs) but with minimal side effects. Bromelain exerts its anti-inflammatory effects via postulated mechanisms involving kallikrein-kinin pathway, cell mediated immunity, and arachidonic pathway (Muhammad and Ahmad, 2017). The kallikrein-kinin pathway involves a reduction of bradykinin and prostaglandin E2 levels at sites of inflammation. Similarly, bromelain activated the factor XII, thereby stimulating pre-kallikrein, and inhibits the formation of thrombus when orally and intravenously administered (Maurer, 2001; Muhammad and Ahmad, 2017).

The anti-inflammatory effects of bromelain could also be induced by the elevation of prostaglandins 1 and 12 levels via the increase platelet cAMP levels (Muhammad and Ahmad, 2017) or happen via the modulation of leucocyte surface constituents (including CD 14, CD 16, CD 21, CD 44 and CD 128) that play significant roles in cellular adhesion, leucocyte homing, stimulation of mediators of inflammation as well as reduction of P-selectin dependent neutrophil recruitment (Hale et al., 2001; Banks et al., 2013). Bromelain inhibited 3T3-L1 in adipogenesis by the reduction of the expression of adipogenic gene and induction of apoptosis as well as lipolysis in developed adipocytes (Dave et al., 2012).

There are evidences that bromelain decreased interferon gamma (INF-γ) with tumor necrosis factor-alpha (TNFα) as well as reduced the deleterious effect of advanced glycaetion end products, thereby controlling inflammation (Stopper et al., 2003). The expression of TGF-beta was modulated by bromelain in individuals with osteomyelofibrosis and rheumatoid arthritis (Rathnavelu et al., 2016). Bromelain stimulates natural killer cells, enhances the production of IL-6, granulocyte macrophage colony stimulating factor (GMCSF), IL-2, and inactivates T-helper cells (Rathnavelu et al., 2016).

The individual complex of bromelain-diosgenin and bromelain-asiaticoside synergistically inhibited phospholipase A2 (Pla2), an enzyme that stimulates inflammation (Mohammed et al., 2018). Elevated levels of Pla2 have been implicated in vascular inflammatory disorders by Shahi et al. (2015).

Erukainure et al. (2011) studied *A. cosmosus* extract's anti-inflammatory activity in gastrointestinal tract and discovered their potential use for the

treatment of ulcerous colitis as well as Crohns disease. Furthermore, they reported that it had the potential to protect the brain tissue. *A. comosus* has anti-rheumatic activity against induced arthritis in rats through oral administration after 21 days (Kargutkar and Brijesh, 2016).

For patients having rheumatoid arthritis and osteomyelo fibrosis, the expression of growth factor is modulated by bromelain. The administration of bromelain to the model of murine of acute asthma, the enzyme functioned to bring about the decrease in the sensitivity and reactivity of the air way to the irritants, induced the reduction of the marker of lung inflammation. In a rheumatoid arthritis rat model, a combination of bromelain and cyclosporine could reduce inflammation and arthritis in concordance to the report of Secor et al. (2008).

Studies have shown that free radicals are responsible for the promotion of the plaque around the artery openings resulting in the accumulation of cholesterol, atherosclerosis, and heart diseases, and causing the spasm of the airway which is capable of inducing asthmatic attack, damaging of vital organs like colon, as well as causing joint pains amongst others. It has also been observed that Vitamin C-rich diets help in the reduction and prevention of the severity (Bamidele et al., 2017).

43.3.9 ANTI-TUMOR EFFECTS

The anti-tumor effect of *Ananas comusus* (pineapple) is attributed to the presence of bromelain. Bromelain consists of enzymes including escharase, peroxidase, acid phosphatase, cellulases, glucosidases. It also contains inhibitors of protease, glycoproteins, and bound calcium (Hale et al., 2005; Amini et al., 2013). According to Hale et al. (2005); Bhattacharyya (2008); and Amini et al. (2013), bromelain is present in all the parts of pineapple, even though bromelain extracted from the stem and fruits were the most investigated (Bhattacharyya, 2008).

Bromelain inhibited cancerous cell growth via different mechanisms, e.g., gastric cancer cell growth by DNA perturbation (Chang et al., 2019). It hinders adhesion, movement, and invasion in glioblastoma cell lines (Tysnes et al., 2001) in addition to activating the extracellular signal regulated kinase (ERK/AKT) process and inhibiting the release of reactive oxygen species (ROS) (Romano et al., 2014). In another study, excess production of ROS induced autophagy which eventually resulted to apoptosis as evidenced by elevated levels of apoptotic induction factor, caspases-3, -8, -9, and Endo G

(Chang et al., 2019). Bromelain induced autophagy-related proteins including LC3-II and also activated autophagosome and lysosome, and thereafter, induced apoptosis in colorectal cancer cells (Chang et al., 2019). Bromelain eliminated MUC1 oncoproteins, which is over expressed in cancerous cells (Yonezawa et al., 2011). This oncoprotein enhances cell transformation, survival of cancerous cell and metastasis and therefore a target of anticancer treatment (Amini et al., 2013).

Bromelain selectively stimulate apoptosis in cancer cells by mechanisms involving, p53 expression, upregulation, and induction of mitochondrial apoptotic route (Rathnavelu et al., 2016). The activities of Akt/ERK were reduced by bromelain. This stimulates apoptosis in tumor cells (Mantovani et al., 2008). Bromelain induced caspase-dependent apoptosis in human gastric cancer cells (MKN45) with anticancer mechanism of bromelain is caused a reduction in the expression of phospho-Akt (Amini et al., 2013).

Apoptosis is required for the maintenance of cellular homeostasis, the loss of its signal, however, is a major contributory factor of cell transformation from normal to cancerous cell. Apoptosis is typified by significant reduction of cell size, chromatin condensation, DNA disintegration, as well as stimulation of caspases (Eckert et al., 1999). Bromelain induced G/M arrest on human carcinoma and melanoma cells by inhibiting nuclear factor-KB (Baez et al., 2007).

The anti-metastatic potentials of bromelain have been reported. Bromelain inhibited cell adhesion proteins (CAPs) required for cell adhesion, migration, and inflammation (Rathnavelu et al., 2016). The anti-metastatic effectiveness of bromelain was established via a mechanism that involved the inactivation of NF-kB. Furthermore, bromelain inhibits cancer invasion by down-regulating the expression of metalloproteinase 9 (MMP-9) (Philchenkov, 2004; Li et al., 2005; Rathnavelu et al., 2016), as well as through down-regulation of activator protein 1 (AP-1) and NF-kB route (Eckert et al., 1999).

The interaction of malignant cells with platelets facilitates angiogenesis. A report showed a significant decline in platelet activation and aggregation upon the administration of bromelain (Garbin et al., 1994). This is explained by bromelain's anti-platelet and proteolytic potentials which culminate in inhibition of platelet-mediated cancer development (Rathnavelu et al., 2016). Angiogenesis is fundamental in tumor growth and metastasis. The anti-angiogenic potentials of bromelain have been reported. The regulation of pro-angiogenic factors including angiopoetin 1 and 2, AP-1, COX-2,

MMP-9, NF-kB, VEGF, and bFGF by bromelain have also been reported (Rathnavelu et al., 2016).

It was also observed that the ethanolic extract of the peel of the plant when taken for about 30 days was able to bring about the lowering of peroxidation of lipids, weight of tumor in breast cancer which strongly suggested that *A. comosus* has anticancer activity. The activity of bromelain is through the decrease in the release of gastric carcinoma Kato cell lines. Therapeutic doses of bromelain can be used for the reduction of excessive coagulation of blood cells, tumor cells growth and reduction in excessive inflammation.

43.3.10 ANTIOXIDATIVE EFFECTS

The antioxidative effect of pineapple is attributed to its flavonoids, triterpenoids, and tannins in addition to bromelain (Vrianty et al., 2019). Ferulic acid, epicatechin, catechin, and gallic acid were reportedly identified in pineapple peel (Li et al., 2014). The crown region of the MD2 pineapple, commonly planted in Malaysia, was detected to contain elevated level of antioxidants (Azizan et al., 2020). The free radical scavenging potentials *A. comosus* core was reported by Rashad et al. (2015).

Different mechanisms were used by the antioxidant activity to mop up the free radicals, stimulate catalase (CAT) activity, oxidative enzymes inhibition and metal chelation. Mhatre et al. (2009) reported that methanol extract of the plant showed the peak antioxidant potential in the DPPH assay. A previous study by Bamidele and Fasogbon (2017) reported that *A. comosus* extract possesses flavonoids and phenolic compounds known to have remarkable antioxidant activity.

43.3.11 ANTI-OBESITY EFFECTS

The global obesity incidence is alarming and requires urgent mediation to curb the disturbing increasing rate of the disease in youths and adolescents. Obesity promotes the development of cardiometabolic disorders like cardiovascular disorders, non-alcoholic fatty liver disease and lowers life expectancy (Garg et al., 2014). The use of traditional and natural remedies for the management of weight gain is gradually gaining momentum especially due to reduced toxicological risk associated with the use of these natural plants or herbs. More so, *Ananas comosus* has been shown to possess the capability to decrease weight gain, lipid accumulation, visceral adiposity,

elevated blood glucose, hyperinsulinemia, hyperleptinemia, and increase circulating adiponectin level in high fat fed rats (El-Shazly et al., 2018). These bioactivities were suggested to be due to its rich bromelain content (El-Shazly et al., 2018). Bromelain was documented to possess proteolytic, lipolytic, and hypocholesterolemic activities (Xie et al., 2014). The statement is in agreement with the past finding of Saxena and Panjwani (2014) on reduced circulating LDL-c, VLDL, and total cholesterol levels in rats with myocardial infraction.

The association between obesity and non-alcoholic fatty liver disease has been established and the expression of glucose transporter 2 has been reported to be elevated in obesity. Interestingly, obesity-induced up-regulation of hepatic GLUT-2 levels driven by insulin resistance has been documented to be linked with the pathogenesis of non-alcoholic fatty liver disease (Gonzalez-Periz et al., 2009). *Ananas comosus* extract was found to decline the elevated hepatic Glut-2 mRNA in obese rat on high fat diet signifying that *A. comosus* may be beneficial in non-alcoholic fatty liver disease treatment (El-Shazly et al., 2018). Furthermore, the polyphenol compounds of *A. comosus* was acclaimed to participate in mediating its anti-obesity activity (Yapo et al., 2011). Hence, *A. comosus* extract mediate obesity by lowering body weight gain, dyslipidemia, and liver fat accumulation in rats fed with high fat diet (El-Shazly et al., 2018). Also, *A. comosus* extract caused reduction in adipocytes number and size (El-Shazly et al., 2018). This action of *A. comosus* extract on the regulation of lipid metabolism may be linked to decreased lipogenesis and elevated fatty acid oxidation (El-Shazly et al., 2018).

43.3.12 ABORTIFACIENT AND UTEROTONIC ACTIVITY

Unripe pineapple has been traditionally acclaimed to have abortifacient potential in various countries like Fiji, the Philippines, Trinidad, Malaysia, and Indonesia. However, hot aqueous extract of ripe pineapple have also been used as arbotifacient in India (Kamboj, 1982). A study by Monji et al. (2016) revealed that both aqueous extract of ripe and unripe *Ananas comosus* have the capacity to cause enhanced uterine myometrial contraction through serotonin 5-HT receptors in rats and the uterus of human. Reports have established that serotonin can cause increased motility of the uterine muscles (Cordeaux et al., 2009) and suggested that the activation of 5-HT2a receptors by *Ananas comosus* could be useful in labor induction in

pregnant women. Conversely, the traditional beliefs that unripe pineapple cause abortion remains a paradox as Yakubu et al. (2011) demonstrated that unripe pineapple do not stimulate abortion. Interestingly, a study by Monji et al. (2016) noted that the ripe rather than the unripe pineapple have a more potent capacity to stimulate uterine contractility resulting in abortion due to elevated level of serotonin.

In folkloric medicine as well as scientific investigations, it has been documented that *A. comosus* has uterotonic effect. It has the potential of inducing labor in pregnant women. Numerous reports showed that both the unripe and the ripe fruit possess this property. The ripe fruits orally administered in traditional medicine induce labor in India (Kerala State), whereas, in Bangladesh, the juice of the unripe fruit was used to induce abortion (Monji et al., 2016).

Monji et al. (2016) reported that fractionated crude ethanolic extract of the plant edible part was potentially effective and impact on the uterine muscles of pregnant rats and humans. Also, Monji et al. (2015) observed that the aqueous extract of pineapple stimulates the uterine wall blocked originally by contractile response brought about by aqueous fractions. In an *in vitro* study, the tocolytic potential of *A. comosus* extract in human uterine and rats were valuable for therapeutic purpose. The transmitter (PhysioTel) was carefully implanted in the rats so as to assess the change in the pressure of the intrauterine wall at *in vivo*. Analyzes were then done through the use of Liquid chromatography. The F2 produced an inhibitory response that was non-selective in nature. The inhibitory potential of the F2 when tested in contraction induced by oxytocin could not be attenuated by propranolol, indomethacin, arginine, and glibenclamide, which also brought about the suppression of the maximal tocolytic potential. The use of a chloride channel inhibitor tends to bring about the suppression of the relaxant impact of the F2. The suppression of the contraction due to oxytocin on Calcium ion solution was suppressed in F2.

Subsequent chemical analysis carried out revealed that citric acid was involved in the tocolytic potential of F2. It was however observed that there was the presence of another less polar component in the production of the inhibitory response observed. It was therefore possible that F2 showed a tocolytic effect through several mechanisms such as antagonizing calcium channel, obstruction of the release of calcium ions intracellularly, and discharge of NO. This corroborated the usefulness of the compound in the formulation of a tocolytic agent (Monji et al., 2018).

43.3.13 ANTIMALARIAL ACTIVITIES

Odugbemi et al. (2008) established that unripe fruits of *A. comosus* could be used in the treatment of malaria. They were able to isolate and characterize some compounds which include glyceryl, dichlorobenzoic acid, diferuloylglycerol, coumaroyl, and tricin.

43.3.14 ANTIHELMINTHIC ACTIVITIES

In North Eastern India, the leaves of the plant (*A. comosus*) have been used traditionally in oral antihelminthic medicine. A study on the antihelminthic potentials of the leaves extract of *A. comosus* was done using the adult earthworm known as *Pheretima posthuma*. The result revealed a dose dependency of the activity which varies with the exposure time (Kataki, 2010). *In vitro* findings revealed that the extract was active when used as an antihelminthic agent against the gastrointestinal nematodes, *Heligmosomoides polygyrus* and *Trichuris muris.*

The extract of *A. comosus* obtained with n-hexane solvent as extractant showed a unique activity against *Comosus luteolus* and *C. tropicals*, but did not show activity against *C. cryptococcus* and *C. rubrum* (Cordenunsi et al., 2010). The aqueous extract showed potency against *Ascaris lumbricoides* and some microscopic worms (Ana et al., 2015). The extract using ethanol from the leaves of *A. comosus* showed antaenicidal and antifilarial potencies (Difonzo et al., 2019).

43.3.15 ANTI-DIABETIC ACTIVITY

Diabetes is a chronic metabolic dysfunction that has severe multi-organs complications. It affects carbohydrate, lipid, and protein metabolism adversely. *Ananas comosus* was reported to improve glucose tolerance in diabetic rats (Riya et al., 2014) by declining glucose level in the blood. Furthermore, it was discovered that *Ananas comosus* also exhibited hypolipidemic effect in diabetic induced rats comparatively to fenofibrate (lipid lowering agent). Interestingly, *Ananas comosus* extract equally elevated circulating HDL-c levels which lend credence to its vasculo-protective potential since high HDL-c level has been linked to reduced incidence of atherosclerosis in diabetes (Taskinen, 2002).

The glucose lowering effects of *Ananas comosus* extract may be due to its ability to enhance peripheral uptake of glucose through tissues of the body. In addition, *Ananas comosus* caused a reduction in LPO signified by reduced circulating, liver, kidneys, and brain levels of LPO marker indicating reduced oxidative stress in these tissues (Xie et al., 2005).

Previous investigations have shown that the extract of *A. comosus* show extreme activity and high potential against diabetic condition at a low concentration as well as high cytotoxicity against hepG2 cancer cells dose dependent pattern (Das et al., 2019**)**. In another study, the finding highlights the efficiency of *A. comosus* extract in area of biomedicine such as in the treatment of serious illness together with in the formulation of drugs used in managing and treatment of diverse diseases like diabetes and cancer (Zharfan et al., 2017).

Oral glucose tolerance examination carried using extract of the *A. comosus* leaves extracted using methanol was used in treating mice at varying doses of 50–400 $mgkg^{-1}$ body weight which revealed a dose dependent decline in the level of glucose in the blood. The decline in the level of glucose was significant when compared to the control. Glibenclamide, an anthyperglycemic drug when used at 10 $mgkg^{-1}$ with respect to body brought about a decline in the blood glucose level by 47.30%. The extract also caused a reduction of abdominal constriction by acetate in mice by 29.60%.

The preliminary phytochemical studies revealed that various bioactive agents such as saponins, alkaloids, tannins, and flavonoids were present in the extract components which also accounted for the observed level of glucose lowering and the analgesic impact.

It was shown that hydroachoholic extract from leaves at 600 mg/kg dose has remarkable antidiabetic potential in diabetic rats induced with streptozotocin (STZ) (Vuyyuru et al., 2020). *A. comosus* exhibits hypoglycemic, hypolipidemic, hepatoprotective, and anti-ulcer effects. Leaf phenols of *A. comosus* decreased fasting blood glucose, low density lipoprotein, glycated albumin, hepatic LPO and increase high-density lipoprotein in rats made hyperlipidemic and diabetic using high fat/high cholesterol diets and alloxan (Xie et al., 2005). One of the possible mechanisms underlying the hypoglycemic property of pineapple may be its influence on glucose metabolism. Ethanolic leaves extract of *A. comosus* had a hypolipidemic effect, that related to inhibiting HMG CoA reductase and from there selectively increased plasma lipoprotein lipase activity (Xie et al., 2007). El-Shazly et al. (2018) while investigating the anti-obesity effect of pineapple reported a decline in serum insulin and upregulation of glut-2 transporter. Pineapple vinegar at 2

ml/kg body weight was shown to suppress serum levels of triglyceride, ALT, alkaline phosphatase (ALP), aspartate transaminase following seven days of acetaminophen exposure by causing a decline in nuclear factor-kappa B (NF-kB), P450 protein expression, and inducible nitric oxide synthase (iNOS) (Mohamad et al., 2015).

43.3.16 COSMECEUTICALS

Prasenjit et al. (2012) reported that the alpha-hydroxy acids from *Ananas comosus* are an important agent in the cosmeceutical industry. These biomolecules can reduce the appearance and rate of formation of skin wrinkles.

Manzoor et al. (2016) reported that bromelain from *Ananas comosus* equally has skin debridement property. Bromelain prevents skin pityriasis lichenoides and scleroderma, which are rare type of skin diseases caused by cutaneous disorder and abnormal growth of connective tissues, respectively.

43.3.17 TOXICOLOGY

An assessment of acute toxicity revealed that the extract of the leaves up to about 5,000 mg/kg administered in the rat through oral pathway did not show signs of toxicity or death in the rat model used. This thereby implies the extract was non-toxic (Debnath et al., 2012).

KEYWORDS

- ***Ananas comosus***
- **bromelain**
- **cosmeceuticals**
- ***Enterobacter cloacae***
- **enterotoxigenic *E. coli***
- **extracellular regulated kinase-2**
- **pineapple**

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CHAPTER 44

A Review on the Medicinal Value of Halotolerant *Rhizophora mucronata* Lam.: A Mangrove Species

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44.1 INTRODUCTION

Rhizophora species are medicinal plants native to Asia's east and southeast. *Rhizophora mucronata*, *Rhizophora mangle*, and *Rhizophora apiculata* are the most prevalent *Rhizophora* species found in mangroves. Mangrove plants are a collection of tropical and subtropical trees and shrubs that thrive near seashores (Tomlinson et al., 1994). *Rhizophora mucronata* Lam. is a small to medium-sized evergreen tree and around 20–25 meters tall. Around the trunk, there are several aerial stilt roots. It has elliptical leaves that are 12 cm long and 6 cm wide. They keep their elongated ends, even though they are quickly fell. The flowers emerge in axillary clusters on the stems, with corky warts on the pale underside of the stems. A cream-colored calyx with four sepals and white hairy petals can be seen on any flower. It has viviparous seeds that start growing while still attached to the tree. The root begins to lengthen and can reach a length of at least a meter. Once the propagule has grown enough to the source under the mud, it is detached from the twig. *Rhizophora mucronata* is found in estuaries, tidal streams, and flat coasts

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sensitive to tidal floods. Its salt tolerance is better than that of other mangrove species, and it creates an evergreen border over mangrove habitats.

Apart from their ecological significance, these plants have another feature that the scientific world is unaware of it, these plant species comprise therapeutic properties. Food and medicine are made from different parts of the *Rhizophora mucronata*. The quantity of several nutrients, such as proteins, lipids, carbohydrates, vitamins, and minerals, has an impact on its utilization (Hardoko et al., 2015).

Rhizophora mucronata was traditionally used as medicine in south Asian countries such as India to treat a plethora of diseases, including diabetes, hepatitis, ulcers, wounds, nausea, hypertension, fever, constipation, leprosy, inflammation, diarrhea, elephantiasis, hematoma, febrifuge, astringent, menstruation disorders and HIV (Sadeer et al., 2019; Batool et al., 2014). Nowadays, scientific literature may challenge these traditional applications since their pharmacological effects, toxicity, usefulness, and safety have not yet been thoroughly explored. Only a few studies have shown its biological effects, including antioxidant (Syaputra et al., 2019), anti-inflammatory (Ray et al., 2016), antimicrobial (Gurudeeban et al., 2016) anti-diabetic (Rohini and Das, 2010), and antiviral properties (Premanathan et al., 1999).

44.2 PHYTOCHEMISTRY

The following bioactive compounds were identified from the leaves of *Rhizophora mucronata*: alkaloids, coumarins, flavonoids, saponins, sterols, terpenes, tannins, glycosides, polyphenols, lipids, inositol, gibberellins, and carbohydrates (Ravindran et al., 2005; Nurdiani et al., 2012; Revathi et al., 2014; Chakraborty et al., 2017). The significant chemical compounds found in *R. mucronata* leaves comprises 2-Furancarboxaldehyde, 5-hydroxymethyl, and 4-hydroxy benzene sulfonic acid (Khattab et al., 2012) as shown in Figure 44.1. The presence of flavonoids has a vital role in plant biochemistry and physiology as antioxidants, enzyme inhibitors, and precursors of toxic chemicals, as well as possessing anti-inflammatory, antioxidant, anti-allergic, and anticarcinogenic properties. Total phenolic content (TPC), total flavonoid content (TFC), total phenolic acid (TPA), total flavanol (TFlavC), condensed total tannins (TTC), and total triterpenoids (TTriC) are total bioactive chemicals found in *R. mucronata* species, and they were identified using colorimetric techniques. The findings were reported as mg of standard chemicals per g of dried extract (gallic acid for TPC; rutin for

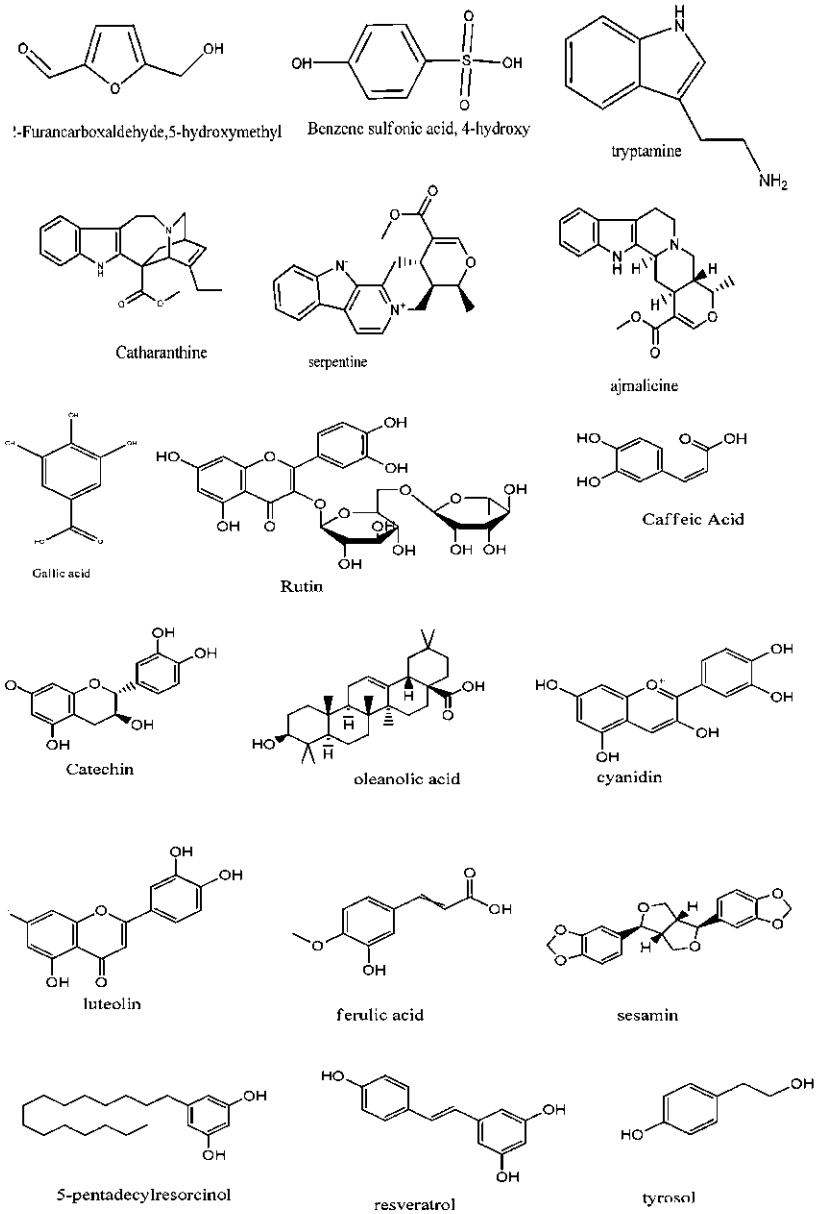


FIGURE 44.1 Some chemical structure of compound represents in above figure like 2-furancarboxaldehyde, 5-hydroxymethyl, 4-hydroxy benzene sulfonic acid, tryptamine, cyanidin, catharanthine, serpentine, ajmalicine, gallic acid, rutin, caffeic acid, catechin, oleanolic acid, cyanidin, luteolin, ferulic acid, sesamin, 5-pentadecylresorcinol, resveratrol, and tyrosol.

TFC; caffeic acid for TPA; catechin for TFlavC and TTC; oleanolic acid for TTriC). Employing ultra-high-pressure liquid chromatography and quadrupole-time-of-flight mass, the untargeted phenolic profile of several *Rhizophora mucronata* extracts was examined (Raut et al., 2014). The results were examined using cyanidin (anthocyanins), catechin (flavanols and flavonols), luteolin (flavones), ferulic acid (phenolic acids), sesamin (lignans), 5-pentadecylresorcinol (alkylphenols), resveratrol (stilbenes), and tyrosol (phenolics) as major phenolic compounds (Sadeer et al., 2019). According to researchers, catharanthine, serpentine, tebersonine, ajmalicine, secologanine, and tryptamine are among the bioactive chemicals identified from *Rhizophora mucronata*. Rhizophorine, an alkaloid, is a major component of *Rhizophora mucronata*'s leaves (Bandaranayake et al., 2002).

44.3 PHARMACOLOGY

44.3.1 ANTIOXIDANT PROPERTIES

An antioxidant is any chemical that delays, inhibits, or eliminates oxidative damage to a target molecule. Antioxidants are oxidation inhibitors, even at low concentrations, and so play a variety of physiological roles in the body. Natural antioxidants can be found in a variety of plant parts, including wood, root bark, leaves, fruit, flowers, seeds, and pollen. Antioxidant elements of plant material operate as radical scavengers, assisting in the conversion of radicals to less reactive forms. According to pharmacological research, *Rhizophora mucronata* is one form of mangrove that has the potential to be a natural antioxidant source (Syaputra et al., 2019). The antioxidant activity of a methanolic extract of different parts of *R. mucronata* was assessed by the scavenging assay, reducing power assay, and total antioxidant. As a result, the leaf extract was found to have stronger antioxidant activity than the bark and root extracts. Furthermore, the total content of phenols and flavonoids in the methanol extracts of the examined species was positively correlated with their antioxidant activities, confirming their significant role in *R. mucronata* antioxidant activity (Kaur et al., 2019). Another *in vitro* antioxidant activity in an aqueous and alcoholic extract of *R. mucronata* bark was evaluated by using various methods, including the DPPH radical scavenging assay, ABTS radical scavenging assay, nitric oxide (NO) radical scavenging assay, ferric reducing assay, and, superoxide radical scavenging assay with IC_{50} values of 110.85, 12.56, 109.06, 193.47, and 88.69 µg/ml for aqueous extract and 59.63, 4.21, 103.21, 242.71, and 84.95 µg/ml, respectively (Selvasundhari et

al., 2014). The ethanolic extract of *R. mucronata* leaves demonstrated strong antioxidant activity, with an IC_{50} of 20.990.33 g/ml (Rumengan et al., 2021). In addition, a comparative study of the antioxidant potential of three different species of mangrove, *Rhizophora mucronata, Rhizophora apiculata,* and *Rhizophora annamalayana,* revealed that *R. mucronata* has a much higher antioxidant potential than the other two species (Arulkumar et al., 2020).

44.3.2 ANTIVIRAL PROPERTY

In vitro antiviral activity of *R. muconata* extract was investigated in terms of inhibition of cytopathic effect (CPE) against the encephalomyocarditis virus (EMCV) on LM (mouse fibroblast) cells. The result of this study was shown that the bark of *R. mucronata* exhibited 100% of CPE inhibition at 12 pg/ml. But, the root of *R. mucronata* is 80% CPE inhibition at 25 pg/ml. while the *in vivo* study was tested in swiss albino mice at the dose of 62.5 mg/kg/day. It was found that bark of *R. mucronata* has shown 30% protection and a 3.21-day increase in average survival time (AST) (Premanathan et al., 1994). Another study examined the antiviral activity of a polysaccharide isolated from the bark of *R. mucronata* using an *in vitro* cell culture system. The anti-HIV activity of the extract was mainly found in the 25–75% ethanol-precipitated fraction. RMP (*Rhizophora mucronata* polysaccharide) protected MT-4 cells against HIV-induced cytopathogenicity and inhibited HIV antigen expression. RMP completely inhibited the viral binding to the cell and the formation of syncytium upon co-cultivation of MOLT-4/HIV-1 IIIB cells and MOLT-4 cells. These results indicate that RMP hindered an early stage of the virus's life cycle (Premanathan et al., 1999). Only a few investigations on *R. mucronata's* antiviral activity have been published yet. As a result, more research into this approach is needed to protect against existing and novel viruses.

44.3.3 ANTIMICROBIAL ACTIVITY

Numerous studies have demonstrated that *R. mucronata* serves as a new potential source of compound producing antibacterial activity against a wide range of bacterial species. Alkaloid-rich leaf extract from *R. mucronata* shown antibacterial activity against two gram-negative bacteria (*E. coli* and *Pseudomonas aeruginosa*) and four pathogenic gram-positive bacteria (*Staphylococcus aureus, Streptococcus pyogenes, Bacillus*

subtilis, and *Streptococcus faecalis*) isolated from type 2 diabetic mediated foot ulcer patients. This study also identified that *Staphylococcus aureus* shown a highest zone of inhibition (19.56 ± 0.19 mm), while *Escherichia coli* shown the minimum zone of inhibition (5.63 ± 0.06 mm) (Gurudeeban et al., 2016). The methanolic leaf extract of *R. mucronata* also shown antibacterial activity against bacterial pathogens such as *V. parahemolytica, K. oxytoca, P. aeruginosa, B. subtilis*, and *K. pneumoniae* (Arunprabhu et al., 2016). Another experimental study reported that almost all parts (leaf, bark, root, flower, and fruit) extract of *R. mucronata* have shown antibacterial activity against both gram-positive bacteria *(S. aureus*) and gram-negative bacteria (*E. coli*). In contrast, a study on the antimicrobial activity of *R. mucronata* fruit extract against human pathogens (*E. coli, S. aureus, M. luteus, T. rubrum,* and *C. albicans)* revealed that the fruit of *R. mucronata* lacked antibacterial activity (Sibero et al., 2020). Other than antibacterial activity methanolic extract of *R. mucronata* also shown antifungal activity against the different fungal strains such as *A. niger, A. flavus, Acremonium* sp., *P. digitatim*, and *Penicillium* sp. (Arunprabhu et al., 2016). Furthermore, studies have demonstrated that *R. mucronata* methanolic bark extract inhibits the growth of the brown rot (*Gloeophyllum trabeum*) and white rot (*Chaetomium globosum*) fungi (Salim et al., 2020). *In vitro* antifungal activity was evaluated using the aqueous and ethanolic leaf extracts of *R. mucronata,* and it was found that the ethanolic extract has shown antibacterial activity against *P. pupurogenome, P. chrysogenum, P. notatum, A. niger, A. alternata,* and *Penicillium italicum* while no antifungal activity was found in the aqueous leaf extract (Somayeh et al., 2017).

44.3.4 ANTI-DIABETIC ACTIVITY

In vivo study showed that a hydro-alcoholic extract of *R. mucronata* leaves was shown to help reduce hyperglycemia in a streptozotocin (STZ)–nicotinamide induced Type 2 diabetes mouse. A significant decrease in the fasting blood sugar level was seen in the treated diabetic rats after repeated application of the hydroalcoholic leaves extracts of *R. mucronata* for 28 days as compared to the diabetic control. This study also suggested that concerning the diabetic control group, extract doses of 200 mg/kg and 400 mg/kg body weight were able to reduce blood glucose levels (Adhikari et al., 2018). Another experimental study showed anti-hyperglycemic activity of *R. mucronata* leaves in Alloxan-induce rats. Alloxan-induced hyperglycemia was observed in rats,

while *R. mucronata* leaves had a dose-dependent antihyperglycemic effect at 100, 200, and 400 mg/kg, similar to glibenclamide. The results of this study demonstrate that after 14 days of injection, the control alloxan-induced rates showed a 350% increase in blood glucose level. When compared to an alloxan-induced control, fresh juice of *R. mucronata* at a dose of 100 mg/kg reduced blood glucose levels by 9.7% within 2 hours, 18.4% at a dose of 200 mg/kg, and 17.5% at a dose of 400 mg/kg. Based on the facts above, it is possible to conclude that *R. mucronata* leaves have anti-hyperglycemic activity (Rohini and Das, 2010).

44.3.5 ANTI-INFLAMMATORY ACTIVITY

Inflammation is a dynamic cellular interaction process that can occur in response to any infectious, injury, or irritation. The modern treatment approach for managing inflammation involves both steroidal and non-steroidal medications (NSAIDs). However, all NSAIDs have the potential to induce major adverse effects such as duodenal ulcers, gastrointestinal hemorrhage, kidney failure, heart attacks, strokes, and so on. As a result, there is a need to find natural substances with higher efficacy of anti-inflammatory and lower toxicity. *R. mucronata* is a popular mangrove plant that has been therapeutically utilized in the treatment of various diseases (Ray et al., 2016). Many scientific studies have shown that *R. mucronata* is a potential source of anti-inflammatory compounds. *In vitro* anti-inflammatory activity of *R. mucronata* leaf, bark, and root extract was evaluated by albumin denaturation, membrane stabilization, and proteinase inhibitory assay. The root demonstrated the highest inhibition (296.26%), followed by the bark (259.48%) and the leaf (237.62%) (Kaur et al., 2018). Furthermore, *in vivo* investigation of *R. mucronata* ethanolic extract demonstrated an anti-inflammatory effect against rodent paw edema in acute and chronic inflammation models. The results of the study showed that ethanolic extract of the leaf at different doses of 100 mg/kg and 200 mg/kg body weight orally shown a reduction in paw edema by 23.077% and 14.615%, respectively after 4 hr. in Carrageenan induced acute inflammatory model while in Freund's adjuvant-induced chronic inflammation model, *R. mucronata* leaf extract shown inhibition in the paw edema 44.44% and 38.89% reduction at two different doses 100 mg/kg and 200 mg/kg, respectively after 28 days (Ray et al., 2016). The methanolic extract of *R. mucronata* bark possesses significant dose-dependent (250 and 500 mg/kg (b.w)) anti-inflammatory activity in formalin-induced

Paw edema, sub-acute pellet induced inflammation, and chronic adjuvant-induced arthritis immunological method in rats.

44.3.6 ANTIDIARRHEAL ACTIVITY

Rhizophora mucronata has been claimed to have a variety of therapeutic characteristics. Traditional medicine in nations such as Burma, India, and China has utilized the bark of *R. mucronata* to cure diarrhea. The scientific study evaluates the effect of *R. mucronata* leaf extract on ileum mobility in rats. In this study, the crude leaf extract of *R. mucronata* was tested on isolated rat ileum. Anti-mobility effect of different concentration ranges between 0.15 and 0.75% of the leaf was tested on methacholine precontracted isolated item. Isolated rat ileum was immersed in an organ bath containing an aerated Tyrode solution. Power Lab recorded the responses of the tissue when it was stimulated with methacholine (10–5M). The extract was applied to the tissue in various concentrations (0.15%, 0.30%, 0.45%, 0.60%, and 0.75%), and the tissue's actions were recorded. The result showed that the extract relaxed or reduced the contractions of isolated rat ileum. The most efficient concentration of *R. mucronata* leaf extract in decreasing ileum motility was 0.50%, which reduced ileum motility by 51.52(%) ± 10.85 by direct action on smooth muscle cells. Furthermore, according to the high-performance liquid chromatography (HPLC) examination, *R. mucronata* leaf extract contains catechin 47.428 ppm and epigallocatechin 3.150 ppm. The findings suggested that the components of *R. mucronata* leaf could be useful in the treatment of gastrointestinal motility issues such as diarrhea (Yunita et al., 2012). Another study also reports antidiarrheal properties of *R. mucronata* bark extracts in which castor oil-induced diarrheal method to assess the activity, the results found that quercetin and caffeic acid reduced the number of wet feces during the 4 h study and anti-diarrheal effects by inhibiting prostaglandins synthesis and due to their antioxidant action (Rohini and Das, 2010).

44.3.7 ANTICANCER ACTIVITY

Cancer is defined as the uncontrolled development and spread of abnormal cells, which is connected with cell cycle regulation and death. Plant-derived compounds are now thought to be the most effective cancer treatment technique. A study found that *R. mucronata* methanolic extract contained carbohydrates, phenol, alkaloid, amino acids, fat, flavonoids, glycosides,

phenols, protein, saponins, sterols, and tannins. The presence of primary, secondary amines, amides, alkanes, alkynes, aldehydes, saturated aliphatic, primary amines, alkyl halides, aliphatic amines, and carboxylic acid was confirmed using Fourier transform infrared spectroscopy (FTIR). The methanolic extract of *R. mucronata* showed potential anticancer activity against the breast cancer MCF-7 cell line. The results of the study observed that at a concentration of 100 g/ml of the extract, the viability of the cell was 90% observed by MTT assay. The viability of the cells was reduced as the concentration of the extract was increased. The cell viability was 50% at a concentration of 1,000 g/ml (Dinesh et al., 2017). Furthermore, the extract was tested for cell viability using a trypan blue dye exclusion assay, and the half-maximal inhibitory concentration (IC_{50}) (1,000 g/ml) value was discovered. Another study observed that polyisoprenoid from *R. mucronata* cytotoxic effect shown against the colon cancer cells (WiDr) (Istiqomah et al., 2021).

44.3.8 ANALGESIC ACTIVITY

The extract of *Rhizophora mucronata* revealed the significant analgesic activity in the acetic acid-induced writhing response in mice in a dose-dependent manner. Intraperitoneally injected acetic acid elicited the visceral pain sensation in the abdomen triggering the localized inflammatory response which increases the pain mediators like prostaglandins especially PGE2, PGF2α, and the lipoxygenase mediated eicosanoids present in the peritoneal fluid, and result in abdominal constriction or writhing in mice. This model is well-established for evaluating peripheral analgesic activity, compounds possessing analgesic activity act on visceral receptors, inhibit the pain mediators, and as a result reduce the number of writhes. RME reduced the writhing response in a dose-dependent manner; therefore it may be suggested that the leaf extract must have peripheral analgesic activity (Kumari et al., 2015).

44.3.9 HEPATOPROTECTIVE ACTIVITY

The liver is thought to play a key role in the metabolism, detoxification, and elimination of xenobiotics from the body. Synthetic medications for liver disease treatment are ineffective and can have major negative effects (Suganthy and Devi, 2016). Traditionally, several plant-based folk medicines have been utilized to treat liver problems. Parts of the *Rhizophora mucronata*

have been shown to have hepatoprotective and antioxidant effects against CCl_4-induced hepatotoxicity in many types of research. Various components of *Rhizophora mucronata* extract were tested for hepatotoxicity in rats (Ravikumar and Gnanadesigan, 2012).

44.3.10 ANTI-ARTHRITIC ACTIVITY

The anti-arthritic activity of *Rhizophora mucronata* (mangrove) extracts is based on the assumption that extract treatment generates various bioactive compounds that may play a role in generating a specific pharmacological activity. The production of autoantigens in some arthritic diseases may be related to protein denaturation and membrane lysis. At 500 mg, the maximum percentage inhibition of protein denaturation, albumin denaturation, and membrane stabilization activity was 97.56%, 90.12%, and 95%, respectively. Studies have shown that extracts of *R. mucronata* are capable of regulating the production of autoantigens and inhibiting protein denaturation, albumin denaturation, and membrane lysis in rheumatic illness. Research findings reveal that methanolic extract of *R. mucronata* leaves has strong anti-arthritic properties and might be a viable source of anti-arthritic activity at different concentrations when compared to the standard drug of diclofenac sodium. The suppression of protein denaturation, albumin denaturation, and membrane stabilization was investigated to determine the mechanism of *R. mucronata's* anti-arthritic action (Kumari et al., 2015).

KEYWORDS

- **bioactives**
- **cytopathic effect**
- **encephalomyocarditis virus**
- **mangrove**
- **protein denaturation**
- ***Rhizophora mucronata***

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CHAPTER 45

Phytochemical and Pharmacological Profile of Sunset Musk Mallow (*Abelmoschus manihot* (L.) Medik.)

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45.1 INTRODUCTION

Abelmoschus manihot (L.) Medik., commonly known as sunset musk mallow or edible hibiscus, belongs to the Malvaceae family. It is an annual or perennial crop that grows up to 2 m tall with herbaceous flowering, and it is mainly grown in southeastern Asia, including China, Indonesia, Nepal, India, New Caledonia, northern Australia, Fiji, and Papua New Guinea (PNG) (Park et al., 2015; Prabawardani et al., 2016). *A. manihot* is commonly called *Aibika* in Indonesian; in Chinese, the common name of *Abelmoschus manihot* is *Huang Shu Kui Hua*. In Korean, it is *Dakpul* and musk mallow or ornamental okra in India. It is a green leafy vegetable with a high micronutrient and high folate content widely consumed in PNG. Totally 140 varieties of Aibika were identified in PNG based on leaf shape and size, leaf palatability, flowering pattern, and stem color. There are 112 accessions of Aibika maintained in the field genebank at the National Agricultural Research Institute (NARI), which was under the vision of the PNG Department of Agriculture, the plants from each accession were yearly replanted (Rubiang-Yalambing et al.,

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2016). The habitat of *A. manihot* is near valleys, fields, grasslands, and sides of ditches. The height of the plant is 2 m, leaves are 10–30 cm in length, and wide, there are 3–9 lobes, the size of the flowers reach up to 4–8 cm in diameter with five petals, the color of petals are white to yellow. The season of flowering is from July to October. The size of the fruit capsule is 5–20 cm long, which contains seeds. *A. manihot* is used as a traditional medicine in China to treat chronic kidney disease (Tsumbu et al., 2012). Various plant parts are extensively utilized to manage chronic bronchitis, inflammation, treat pain and renal diseases (Rubiang-Yalambing et al., 2016; Kim et al., 2018). The different parts of *Abelmoschus manihot* like leaves, flowers, and stems consists of various bioactive components and pharmacological activities. So the researchers widely worked on the pharmacological effect of *A. manihot*, including anti-inflammatory, antidiabetic, neuroprotective, and ulcerative colitis.

45.2 BIOACTIVES

The chemical compounds identified from *Abelmoschus manihot* flower are divided into different groups: flavonoids, polysaccharides, steroids, amino acids, nucleosides, and volatile oils. Flavonoids, the secondary metabolites, were purified from the plant extract using high-performance chromatography. The total flavones have a significant effect on various diseases, flavonoids namely hibifolin, hyperoside, isoquercitrin, quercetin-8-3'-O-β-glycopyranoside, and 3-O-robinobioside (Yan et al., 2015). There are nearly 22 amino acids reported from the *A. manihot* roots, stems, and leaves. The amino acids play a vital role in whole-body mechanism, it is involved in lipid transport and neurotransmission, in addition, it has pharmacological activities (Zhang et al., 2015). The essential biological compounds involved in many physiological processes, namely nucleotides, nucleosides, and nucleobases, were identified from the plants, such as nicotinamide, thymine, adenine, cytidine guanine, thymidine, uracil, and guanosine. These components have significant bioactive and nutraceutical properties (Du et al., 2015). A few polysaccharides were found from the ethanolic extract of *Abelmoschus manihot*; the polysaccharides mainly consist of glucose, mannose, galactose, and fucose (Zheng et al., 2016). Further, some organic acids, sterols, and volatile compounds were identified from the different parts of plants. Few compounds identified in the plant is given in Figure 45.1.

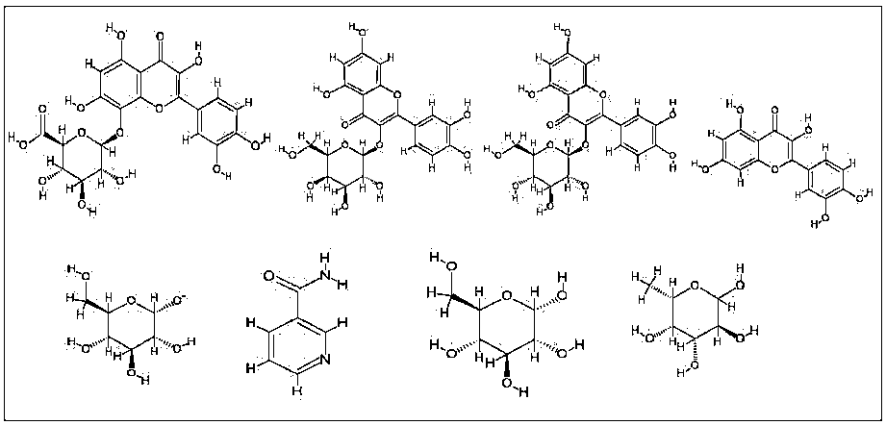


FIGURE 45.1 The chemical compounds identified from *Abelmoschus manihot* flower are hibifolin (1), hyperoside (2), isoquercitrin(3), quercetin (4), -O-b- glycopyranoside (5), nicotinamide (6), Glucose (7), and Fucose (8) [*Source:* Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures].

45.3 PHARMACOLOGY

Abelmoschus manihot being used as a traditional medicine as well as vegetable in local areas, has significant pharmacological activities such as anti-inflammatory, renoprotective activity, antioxidant, antitumor, gastroprotective, and ulcerative colitis. In many studies, the ethanolic extract of *A. manihot* flower is used to treat various diseases and pain. The different parts of a plant consist of flavonoids, amino acids, organic acids, and sterols. These components have biological properties and pharmacological activities. Even though some studies proved, it has low toxicity in further it would be investigated the toxicological and side effects of the plant may be useful in formulating drugs.

45.3.1 ANTI-INFLAMMATORY ACTIVITY

The methanol and petroleum extract of *Abelmoschus manihot* woody stems prepared at three different doses such as 100, 200, and 300 mg Kg^{-1} were used to determine the anti-inflammatory activity in a rat model. The woody stems extract has a significant anti-inflammatory role against the rat model of carrageenan and histamine-induced paw edema compared to standard drug diclofenac sodium 10 $mgKg^{-1}$ (Jain et al., 2010). The ethanol extract of *A.*

manihot alleviates dextran sulfate sodium-induced colitis in mice by altering gut microbiota composition, enhancing microbial diversity, and affluence the gut microbiota, producing straight-chain fatty acids (SCFAs) that subsequently increase the level of butyrate and acetate. Further, the *A. manihot* ethanolic extract was treated to the DSS group with or without AM treatment in mice, cause an increased level of proinflammatory cytokines (TNF, IL-17, IL-22, IL-6, and IL-1b) in the DSS group. In contrast, a decreased level of proinflammatory cytokines was observed under AM treatment. Similarly, chemokines (CCl-2, CXCL-2, CXCL-1, CXCL-9, and CXCL-10) and adhesion molecule levels decreased in the AM treatment. The imbalance of Th17/Treg was regulated through the activation of the PPARg signaling pathway mediated by butyrate, which reduced colitis inflammation (Zhang et al., 2019).

45.3.2 ANTIDIABETIC NEPHROPATHY ACTIVITY

The *Abelmoschus manihot* capsule/Huangkui capsule (HKC) at a dose of 2 g/kg/d enhance the general status, alleviated proteinuria, albumin, glomerulosclerosis, and renal histological changes in the rat model in two groups (unilateral nephrectomy and doxorubicin-induced nephropathy), whereas it decreases the infiltration and activation of ED_{1+} and ED_{3+} macrophages in glomeruli and suppresses the expression of tumor necrosis factor (TNF)-α protein in the kidney. In addition, HKC down-regulated the p-p38MAPK and transforming growth factor (TGF)-β1 protein expression, consequently inhibiting the p38MAPK signaling pathway activity (Zhao et al., 2012; Tu et al., 2013). The effect of HKC and α-lipoic acid (LA) at a dose of 0.75 and 2 g/Kg was studied on rat groups after induced diabetic nephropathy by unilateral nephrectomy with STZ. The general status of rats, body weight, urinary albumin, kidney weight, renal function was improved in HKC and LA treatment. In addition, the HKC reduced the level of serum uric acid, blood urea nitrogen and thereby mitigated kidney fibrosis by decreasing the extracellular matrix in glomeruli. In contrast, it increased the superoxide dismutase (SOD), malondialdehyde (MDA), nicotinamide adenine dinucleotide phosphate oxidase-4, and 8-hydroxy-2-deoxyguanosine. The AM treatment involves in molecular mechanism; it reduces the protein expression of p-Akt, pp38MAPK, TNF-a, and TGF-b1 through inhibition of the p38MAPK and Akt signaling pathway (Mao et al., 2015).

45.3.3 GASTROPROTECTIVE ACTIVITY

The flowers of *Abelmoschus manihot* was used to treat gastric ulcers; the study reported that the gastric ulcer was induced in mice using oral administration of ethanol. The effect of total flavones of *A. manihot* (TFA) was studied compared with the standard drug omeprazole (100 mg/Kg). Superoxide dismutase and glutathione (GSH) activity increased after being treated with TFA, whereas the MDA level decreased. In addition, the expression level of *TNF-α, Bax, and NF-kB(p65)* decreased, and the regulated Bcl-2 expression was reported in mice (Zhang et al., 2020).

45.3.4 ULCERATIVE COLITIS

Abelmoschus manihot (AM) flower extract has been used to study the therapeutic effect on ulcerative colitis in mice; mice induced with 2.5% dextran sulfate sodium and treated with the *A. manihot* extract. Disease activity indexes were calculated by monitoring the body weight, water consumption, and diarrhea during the experiment. The protein expression of caspase-1, p10, ZO-1, ASc, NLRP3, claudin, and occludin were determined. The mice treated with AM reduced the mortality rate of mice, decrease colon damage and splenomegaly. In addition, the level of proinflammatory cytokines (Il-7, IL-6, IL-8 < IL-1β, and TNF-α) were decreased, whereas it improves the level of interleukin-10. AM treatment regulated the protein expression and mRNA level in mice; it has a therapeutic effect against UC, which may involve the inflammasome signaling pathway (Wu et al., 2021).

45.3.5 ANTICONVULSANT AND ANTIDEPRESSANT ACTIVITY

Depression changes in mood, behavior, appetite, and energy; it is also associated with a psychiatric disorder (Nemeroff, 2007). The oral administration of 200 mg/kg dose ethanolic extract of *Abelmoschus manihot* flower to the pentylenetetrazole (PTZ) induced clonic convulsions in mice. The study demonstrated that AM treatment reduced the mortality rate and prolonged lifetime. However, the latency time was non-significant when compared with fluoxetine (20 mg/kg) (Guo et al., 2011). Further, the total flavones of *Abelmoschus manihot* were used to study post-stroke depression in rats. The expression of corticotropin-releasing factor (CRF) and mRNA in the hypothalamus and consumption of sucrose were observed. As a result, TFA (50,

100 mg/kg) improved SOD, GPX whereas the MDA level was decreased when compared with fluoxetine (1.8 mg/kg). The downregulation of CRF decreased optical density values of CRF positive neurons and improved sucrose drinking in rats (Luan et al., 2020).

45.3.6 ANTITUMOR ACTIVITY

The polysaccharide extracted from the *Abelmoschus manihot* supplemented at a range of 50 to 400 mg/mL downregulated the proliferation of gastric cancer cells and hepatic carcinoma cells in humans (Zheng et al., 2016). The bioactive compounds such as hyperoside, 8-(2″-pyrrolidone-5-yl)-quercetin, cannabiscitrin, and 3-O-kaempferol-3-O-acetyl-6-O-(p-coumaroyl)-b-D-glucopyranoside improve the differentiation of pre-osteoblast MC3T3-E1 cells when the HKC supplementation at 0.05 and 5 mM. In addition, 3-O-kaempferol-3-O-acetyl-6-O-(p-coumaroyl)-b-D-glucopyranoside decrease the proliferation of myelomaARP1 and H929 cells. Moreover, the HKC concentration at 3.75 g/kg/day extended the survival rate of mice prone to multiple myeloma (Hou et al., 2020).

KEYWORDS

- ***Abelmoschus manihot***
- **Huangkui capsule**
- **Sunset Musk mallow**
- **antitumor activity**
- **transforming growth factor**
- **tumor necrosis factor**

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Former Professor, Department of Botany, Sri Krishnadevaraya University, Andhra Pradesh, India

T. Pullaiah, PhD, is a former Professor at the Department of Botany at Sri Krishnadevaraya University in Andhra Pradesh, India, where he has taught for more than 35 years. He has held several positions at the university, including Dean of the Faculty of Biosciences, Head of the Department of Botany, Head of the Department of Biotechnology, and Member of Academic Senate. Under his guidance, 54 students earned their doctoral degrees. He was President of the Indian Botanical Society (2014), President of the Indian Association for Angiosperm Taxonomy (2013), and Fellow of the Andhra Pradesh Academy of Sciences. He was awarded the Panchanan Maheshwari Gold Medal, the Prof. P. C. Trivedi Medal, the Dr. G. Panigrahi Memorial Lecture Award of the Indian Botanical Society, and Prof. Y. D. Tyagi Gold Medal of the Indian Association for Angiosperm Taxonomy, and the Best Teacher Award from Government of Andhra Pradesh.

A prolific author and editor, he has authored 52 books, edited 23 books, and published over 330 research papers. His books include *Advances in Cell and Molecular Diagnostics* (published by Elsevier), *Camptothecin, and Camptothecin Producing Plants* (Elsevier), *Ethnobotany of India* (5 volumes, published by Apple Academic Press), *Global Biodiversity* (4 volumes, Apple Academic Press), *Red Sanders: Silviculture and Conservation* (Springer), *Genetically Modified Crops* (2 volumes, Springer), *Monograph on Brachystelma and Ceropegia in India* (CRC Press), *Flora of Andhra Pradesh* (5 volumes), *Flora of Eastern Ghats* (4 volumes), *Flora of Telangana* (3 volumes), *Encyclopedia of World Medicinal Plants* (7 volumes, 2nd edition), and *Encyclopedia of Herbal Antioxidants* (3 volumes). He is currently working on 36 volumes of the new book series *Biodiversity Hotspots of the World*.

Professor Pullaiah was a member of the Species Survival Commission of the International Union for Conservation of Nature (IUCN). He received his PhD from Andhra University, India, attended Moscow State University, Russia, and worked as postdoctoral fellow during 1976–1978.

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Abbreviations

5-FU	5-flucytosine
AAL	*Acalypha australis*
ABTS	2,2-azobis-3-ethylbenzthiazoline-6-sulfonic acid
ACA	1′-S-1′-acetoxychavicol acetate
ACE	angiotensin-converting enzyme
AChE	acetylcholinesterase
ACP	acid phosphatase
ADP	Adriamycin
AFB1	aflatoxin B1
AGEs	advanced glycation end products
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMP	adenosine-5-monophosphate
AMPK	adenosine monophosphate-activated kinase
APRT	adenine phosphoribosyltransferase
AST	aspartate aminotransferase
Aβ	amyloid-β
BALF	bronchoalveolar lavage fluid
B-ALL	B-cells acute lymphoblastic leukemia
BCT	Boyden chamber technique
BDMC	bisdemethoxycurcumin
BET	biopolymeric fraction
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
BMA	*Butea monosperma* agglutinin
BPH	benign prostatic hyperplasia
BSPD	bovine serum protein denaturation
CACO	colorectal carcinoma
CAT	catalase
CB	*C. baccifera*
CCl_4	carbon tetrachloride
CD	cardiac damage
CDK1	cyclin dependent kinase-1
CE	chloroform extract

CFA	complete Freund's adjunct
CIS	chronic immobilization
Cl	chloride
CLA	conjugated linoleic acid
CMC	carboxyl methylcellulose
CNS	central nervous system
COX	cyclooxygenase
DAP	*Dendrobium aphyllum* polysaccharide
DCM	dichloromethane
DENA	diethyl nitrosamine
DHHDP	1-galloyl-2,3-dehydrohexahydroxydiphenyl
DLA	Dalton's lymphoma ascites
DM	diabetes mellitus
DPPH	2,2-diphenyl-1-picrylhydrazl
DTH	delayed-type hypersensitive
E-1	endothelin-1
EAC	Ehrlich ascites carcinoma
EAD	egg albumin denaturation
EAE	ethyl acetate
EBV	Epstein-Barr virus
EBV-EA	Epstein-Barr virus early antigen
EC	epicatechin
ECG	epicatechin gallate
EE	ethanolic extract
EGC	epigallocatechin
EGCG	epigallocatechin gallate
Eh	*E. hirta*
EMT	epithelial-mesenchymal transition
EOs	essential oils
EPO-R	erythropoietin receptor
ER	estrogen receptor
ERK	extracellular signal-regulated kinase
FAB-M	fast atom bombardment mass spectrometry
FRAP assay	ferric reducing/antioxidant power assay
FRAP	ferric reducing ability of plasma
FRSA	free-radical scavenging activity
FSS	forced swim stress
G6Pase	glucose-6-phosphatase
GABA	gamma-aminobutyric acid
GC	gas chromatography

GC-MS	gas chromatography-mass spectrometry
GKRP	glucokinase regulatory protein
GLUT4	glucose transporter 4
GSH	glutathione
GTP	green tea polyphenols
GUI	gastric ulcer index
HAEPA	hydro-alcoholic extract of leaves of *P. amarus*
HAP	hydroxylapatite
HCV	inhibit hepatitis C virus
HDE	hydro-defatted extract
HDL	high-density lipoprotein
HE	hexane
HE	hexane extracts
HE	hydro extract
HF	high-fructose
HFD	high fat diet
HFSSD	high-fat sugar salt diet
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HIV	human immunodeficiency virus
HK	hexokinase
HMGCoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HMP	7-(4′-hydroxy-3′-methoxyphenyl)-1-phenylhept-4-en-3-one
HSV	herpes simplex virus
HUVECs	human umbilical vein endothelial cells
i.g	intragastric
i.m	intramuscular
i.p	intraperitoneal
i.v	intravenous
IFN-γ	interferon-gamma
IGR	insect growth regulators
IL-1β	interleukin-1β
iNOS	inducible nitric oxide synthase
IR	insulin resistance
JNK	c-Jun N-terminal kinase
K	potassium
LH	luteinizing hormone
L-NAME	N^G-nitro-L-arginine methyl ester
LOX	lipoxygenase
LPO	lipid peroxidation
LPS	lipopolysaccharide

MAPK	mitogen-activated protein kinases
MB	methyl brevifolincarboxylate
MBC	minimum bactericidal concentration
MCP-1	monocyte chemotactic protein
MDA	malondialdehyde
MDR	multidrug resistance (μg)
ME	methanol extract
MEAL	methanol extract *Acalypha australis*
MEDC	methanol extract *Dianthus chinensis*
MEPA	methanol extract *Pteridium aquilinium*
METR	methanol extract of *T. rhomboidea*
MIC	minimum inhibitory concentration
MMP-3	matrix metalloproteinase-3
MOTT	*Mycobacterium* other than tuberculosis
MPO	myeloperoxidase
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	mass spectrometry
MST	median survival time
MTB	*Mycobacterium tuberculosis*
mTOR	mammalian target of rapamycin
Na	sodium
NDEA	N-nitrosodiethylamine
NF-κB	nuclear factor-κB
NMR	nuclear magnetic resonance
NO	nitric oxide
NSCLC	non-small cell lung cancer
PAF	platelet-activating factor
PBMC	peripheral blood mononuclear cell
PCA	passive cutaneous anaphylaxis
PCNA	proliferating cell nuclear antigen
PGE2	prostaglandin E2
P-gp	P-glycoprotein
PI3K	phosphatidylinositide 3-kinases
PII	primary irritation index
PKC-δ	protein kinase
PPAR	proliferator-activated receptor
PPi	inorganic pyrophosphate
PRPP	a-d-5-phosphoribosyl-1-pyrophosphate
PSD	postsynaptic density

ROS	reactive oxygen species
RSV	respiratory synthetical virus
RT	reverse transcriptase
SA	*S. alternifolium*
SD	standard diet
SDA	Sabouraud dextrose agar
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMA	smooth muscle actin
SOD	superoxide dismutase
SRBC	sheep red blood cells
STD	seminiferous tubular diameter
STZ	streptozotocin
TAZ	transcriptional co-activator with PDZ-binding motif
TC	total cholesterol
TGF	transforming growth factor
TLC	thin-layer chromatography
TLR2	toll-like-receptor-2
TNF	tumor necrosis factor
TOSC	total oxy radical scavenging capacity
TP	total protein
TPA	12-O-etradecanoylphorbol-13-acetate
TRE	tree root extract
TTC	2,3,5-triphenyl tetrazolium chloride
USE	ultrasonic-assisted solvent extraction
VEGF	vascular endothelial growth factor
WA	*Wrightia arborea*
WAD	West African dwarf
WE	water extracts
WUE	water use efficiency
XPRT	xanthine phosphoribosyltransferase

Preface

Many young researchers used to approach me with the question, 'Can you suggest me a medicinal plant on which I can work?' To answer this question, I had to dig out the literature on the bioactives and pharmacology of medicinal plants. During this search, I found that a comprehensive review of Phytochemical composition and pharmacy for many medicinal plants is not available. With a view to filling this gap, we started this series of 10-volume book series on Bioactives/Biomolecules/Phytochemistry and Pharmacology of Medicinal plants. This is the last book in this series. A comprehensive review of more than 80 plant species is given in this two-volume book.

In each chapter, a brief introduction about the species is given. Bioactive phytochemicals from the plant are then listed, and their chemical structures are given. It is followed by Pharmacological activities. All the published literature on the pharmacological activities of that species is reviewed. A wide array of biological activities and potential health benefits of the medicinal plant, which include antiviral, antimicrobial, antioxidant, anti-cancer, anti-inflammatory, and antidiabetic properties, as well as protective effects on the liver, kidney, heart, and nervous system, are given.

Many contributors to this book are young researchers, mostly research scholars. In many cases, the manuscripts have been revised three to four times. Publishers insisted on bringing down the plagiarism to 5%, which was a tough task because chemical names, disease names, and methods couldn't be modified. In spite of this, plagiarism was brought down to nearly 5%. I thank both publishers and contributors for the same.

I hope that this will be a sourcebook for the development of new drugs. I request the readers to give their suggestions for improvement of the coming volumes and the next edition.

I wish to express my grateful thanks to all the authors who contributed to the review chapters.

CHAPTER 46

An Overview of Pharmacological Properties and Bioactives Principles in Indian Mallow [*Abutilon indicum* (L.) Sweet]

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46.1 INTRODUCTION

Abutilon indicum is known as country mallow, which belongs to the Malvaceae family. It is widely called by different names like *Atibala* in Sanskrit, *Thuthi* in Tamil, *Kangi/Kakahi* in Hindi, *Dabi* in Malayalam, and *Tuttura-benda* in Telugu (Rajeshwari and Sevarkodiyone, 2019). They are native to South Asia, and it is a weed where they disseminated to several countries like India, Sri Lanka, the Philippines, and Indochina (Goyal et al., 2009). The plants have taproots and a smooth surface with a diameter of 1.2–1.5 cm. The flowers are yellowish with a mild fragrance. Stipulate, cordate, and evergreen leaves are seen. Leaves are 2–2.5 cm with a sharp curve (toothed) and acuminate type, dorsiventral. Stems are usually 2–3 m tall with numerous branches and glorifying stem surfaces. Fruits also have a shiny surface and possess a capsule type. Seeds are of size 3–5 mm and black to brown in color (Patel and Rajput, 2013). This plant has phytochemicals extracted and used for medicines like tuberculosis, cold, cough, bronchitis, fever, diabetes, stomach-related problems, and even mumps. Some evidence showed that plant juice cures jaundice against some microbes (Abdul et al., 2010).

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Phytoconstituents present in the plant have β-sitosterol, phenolic acids that help cure upper tract respiratory infections; used in the preparation process of '*Madhusyashtyadi syrup*,' an ayurvedic medicine. Seeds can also be used in treating coughs. Bark and roots are used as a nervine tonic, antidiabetic, diuretic, and aphrodisiac. Decoction of leaves is used in the treatment of tender gums and toothache (Kailasam, 2015).

46.2 BIOACTIVES

The plant possesses important bioactive compounds like alkanols, β-sitosterol, amino acids, fumaric acids, p-coumaric, vanillic, alanto-lactone, n,n-alkane mixtures, and iso-alantolactone (Rajeshwari and Sevarkodiyone, 2019). Reports indicate that the ethanolic extract (EE) of leaves has 72% of quercetin more than in flowers. Mucilage, tannins, organic acids, sterols, alkaloids, triterpenoids, magnesium phosphate, chlorides, calcium carbonate, alkaline sulfates, α-tocopherol, and β-sitosterol, are isolated from leaves. Aerial parts of the plant have histidine, fructose, gluco-vanilloyl glucose, aspartic acid, threonine, leucine, serine, fumaric acid, vanillic acid, and p-hydroxybenzoic acid. Gallic acid, asparagine, β-amyrin, terpenes, steroids, flavonoids, and terpenoids are present in the root portion of the plant. The mucilage fraction of roots are reported to have galactose and galacturonic acid. The flower has the occurrence of bioactive compounds like cyanidin-3-rutinoside, 7-gossypetin, and 8-glucosides. Isoalantolactone and alanto-lactones are two types of sesquiterpene lactones seen in flowers. Studies indicated that flower has the presence of flavonoids viz, quercetin 3-O-α rhammopyranosyl (1-6)-β glucopyranoside, luteolin, chrysoreiol-O-β-glucopyranoside and quercetin-3-O-β-glucopyranoside, apigenin 7-O-β-glucopyranoside. Essential oils (EOs) obtained from flowers have bioactive compounds like geraniol acetate, α-geraniol, α-pinene, tetradecane, and geraniol; bioactives present in the seed can be identified by methods of periodate oxidation, methylation, acid-catalyzed fragmentation. It showed that the seed had linked mannopyranosyl units with a linear chain of β-D (1-4). Compounds like glycine, glutamine, threonine, serine, lysine, proline, lystenine, phenylalanine, and asparagine are also present in the amino acid structure of seeds. Palmitic and stearic acids are present. Alkaloids and flavonoids are present in the fruit portion. From the whole plant, some compounds are reported like taraxasterol, luperol, sitosterol, kaempferol, abutilin A, p-β-D-glucosyloxybenzoic acid, (R)-N-(1′-methoxycarbonyl-2′-phenylethyl)-4-hydroxybenzamide (Patel and Rajput, 2013). Overall, it has 28 known bioactive compounds viz, two

amides, 12 benzenoids, three alkaloids, three coumarins, four nucleosides, two steroids, and two ionones (Kuo et al., 2008). Methanolic extracts of the plant have anti-fertility substances and laxative substances (Edupuganti et al., 2015). Seeds also have linolenic acid, linoleic, and oleic acids. Gossypetin-8-glucoside and cyanidin-3-rutinoside were identified from the petals of *Abutilon indicum* (Gaind and Chopra, 1976). A few important chemical compounds of *Abutilon indicum* are represented in Figure 46.1.

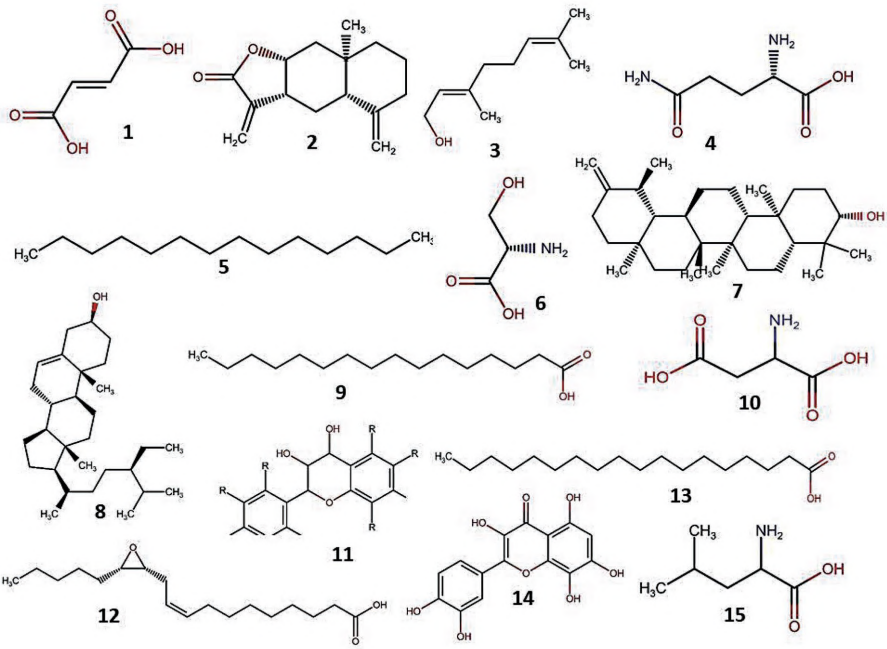


FIGURE 46.1 The chemical structure for the bioactive compounds in *Abutilon indium*. Fumaric acid (1); isoalantolactone (2); geraniol (3); tetradecane (4); glutamine (5); serine (6); tarakasterol (7); β-sitosterol (8); palmitic acid (9); aspartic acid (10); leucoanthocyanidin (11); vernolic acid (12); stearic acid (13); gossypetin (14); and leucine (15).

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

46.3 PHARMACOLOGICAL ACTIVITIES

46.3.1 ANTI-DIABETIC ACTIVITY

In a study to prove the antidiabetic effect of *Abutilon indicum*, Wistar rats (male) were fed with a standard pelleted diet. Streptozotocin (STZ)

was injected intraperitoneally into the rats to induce diabetes. These diabetic rats were divided into four groups. Teat group rats are fed with glibenclamide and crude extracts of *Abutilon indicum*. Results show that postprandial plasma concentrations of glucose were significantly reduced when treated with crude extracts of *Abutilon indium*. In addition to this, crude extract of the plant was found in activating glucose transporter promotion activities. At the same time, it does not affect the activity of kinases involved in GSK-3β and Akt pathways. This plant has helped maintain adipocyte differentiation through PPARγ and increases the utilization of glucose, which mainly helps decrease insulin resistance (IR) (Krisanapun et al., 2011).

The EE of the plant chloroform fraction was prepared to study the anti-diabetic effects. In Sprague Dawley rats (males), STZ was intraperitoneally injected to induce diabetes in rats. Six rats from each group were divided and fed accordingly. The radioimmunoassay method was used to examine the serum insulin levels after the rats had been fed with the chloroform extracts (CEs) of the plant at a dose of 50 mg/kg, resulting in reduced blood sugar levels compared with the standard control. There were significant changes in serum insulin, serum lipid profiles, hemoglobin levels, and glycosylated hemoglobin compared with the other diabetic controls. The active compounds separated from the plant extracts and developing them as potential antidiabetic substances are efficient. A dose of 50 mg/kg of chloroform fraction resulted in a decrease in blood glucose levels within 30 minutes compared with glucose-loaded control (Kaushik et al., 2010). When alcoholic and aqueous extracts of the plant were administered orally at a dose of 400 mg/kg resulted in decreased blood glucose levels to 26.95% and 23.20% within 4 hrs. Whereas different extracts have shown hypoglycemic activity, aqueous extracts were more efficient in reducing blood glucose levels. D-400 herbomineral preparation was made from the seed powder of *Abutilon indicum*, which proved to be an excellent adjuvant to hypoglycemic agents' oral feeding, reducing side effects (Mangla et al., 2012). Another test was conducted with methanolic extracts of *A. indicum;* STZ-treated diabetic Wistar rats were orally fed with 500 mg/kg for a single time, resulting in decreased blood glucose levels after 2 hrs. of administration. Blood glucose concentration in postprandial elevation after providing glucose as a feed suppresses the blood glucose level in animal models. *In vitro* studies showed that the extract of *A. indicum* suppressed the disaccharide-digesting enzymes and α-glucosidases in the small intestine (Adisakwattana et al., 2009).

46.3.2 WOUND HEALING ACTIVITY

Abutilon indicum has the property to cure wounds proved by dead space, excision, and incision studies. For this, Wistar albino rats and Swiss albino mice were used. These rats were given anesthetized and shaved. On the dorsal thoracic region of the rat, a circular wound of 2 cm was made (excision models); for the incision model, anesthesia was given with ether, and the vertebral incision was made of 6 mm. Sutures were done using silk thread. By implanting the polypropylene tube, a dead space is made. Usually, wound healing takes several steps, starting with the acute inflammation phase to the synthesis of collagen and the formation of scars. A drug that works in one phase does not act in another phase. *Abutilon indicum* has helped the extensive growth of granulation tissue; the wound has healed completely with the standard architecture of reticulin and collagen. This plant increases collagen synthesis. EEs of *A. indicum* have a swift increase in skin tearing strength, dry granuloma weight, granuloma strength, and wound contraction rate, resulting in decreased epithelization (Roshan et al., 2008). Another study stated that petroleum ether extract made from the plant has more wound healing capacity than EE. Petroleum ether extract showed a rise in wound closure rate when monitored daily after injecting *A. indicum* extract (Kailasam, 2015).

46.3.3 HEPATOPROTECTIVE EFFECT

The liver is an organ that purifies toxic substances, so care for the liver is much essential. *Abutilon indicum* has hepatoprotective activities. Adult Charles Fuster rats (150–180 gm) were the animal model used. The rat model was divided into several groups; one group was fed with olive oil as standard control and the other with toxicant control by inducing liver damage by carbon tetrachloride (CCl_4) along with olive oil; Another group received Liv-52 which acts as a standard drug for liver damages, and the remaining groups are administered with carbon tetrachloride and different doses of *Abutilon indicum* extract (100, 200, 400 mg/kg) for 10 days. After the experiment, the animal models were sacrificed and analyzed for liver damage. The result showed that plant extract exhibited hepatoprotective activities by reducing the liver damage caused by carbon tetrachloride, equal to the chemical standard drug Liv-52 against liver damage (Sharma and Sahu, 2016). In a study with Wistar albino rats weighing 150–200 mg, carbon tetrachloride and paracetamol were used to induce liver damage; rats

induced with liver damage were treated with *Abutilon indicum* hydro-extract, 100 and 200 mg/kg and silymarin (100 mg) as a standard drug against liver damage. The results depicted that *Abutilon indicum* extract reduced the damage level from 800–360 at 100 mg/kg dose level, and around 800–290 at 200 mg/kg of dose level (Porchezhian and Ansari, 2005). Female albino rats (150–200 mg) fed with *A. indicum* extracts reported positive effects by reducing the damage in the liver (Revansiddaya et al., 2011).

46.3.4 ANTI-ULCER ACTIVITY

In a study, albino rats weighing 100–200 g were chosen as animal models, and the gastric ulcer was induced by ethanol and pyrrolic ligation. A group served as a control, and another was administered with omeprazole (20 mg/kg bw). The remaining groups were fed with *Abutilon indicum* ethanolic plant extracts from 200–400 mg/kg. After these examinations, results indicated a reduction in gastric ulcer index (GUL) in the groups of rats treated with *Abutilon indicum* plant extracts and omeprazole standard drug (Venkateswarlu et al., 2015). Another study showed that methanolic extract of *Abutilon indicum* plant extracts of 250–500 mg/kg reduces GUL, acidity, and gastric volume compared with the standard drug ranitidine (50 mg/kg); results prove *A. indicum* is used for treating ulcers show a potent anti-ulcer activity (Dumantraj et al., 2005). When the animal model was induced with ulcers with acetic acid and ethanol, *Abutilon indicum* had positive effects. The standard drug famotidine 20 mg/kg bw. was used (Shekshavali and Roshan, 2016).

46.3.5 ANTI-ASTHMATIC ACTIVITY

Asthma is prevalent due to numerous factors which pollute the air. These dust and air pollution are the foremost reasons for asthma. In an experiment, guinea pigs (400–600 g) were divided into different groups by inducing asthma treated with histamine and acetylcholine, where one group of pigs was taken as control, by treating with carboxymethylcellulose, another with ketotifen, a standard drug close to 1 mg/kg. The remaining groups were treated with *Abutilon indicum* methanolic extracts of 250 and 500 mg/kg. The bronchi and trachea were analyzed after the dosing, demonstrating that *Abutilon indicum* extracts reduced the bronchitis levels nearly equal to a chemical drug ketotifen, proving that *Abutilon indicum* effectively treats

asthma (Paranjhape and Mehta, 2006). Humans of age groups from 15–80 yrs. by following safety practices and precautionary measures. The persons affected with mild asthma were treated with *Abutilon indicum* extract; the examinations and results reduced the severity of asthmatic symptoms. The person who suffocated from asthma was able to breathe freely. This plant extract replaced several chemical drugs for the treatment of asthma (Paranjape and Mehta, 2008).

46.3.6 ANTI-MICROBIAL ACTIVITY

Abutilon indicum is also known for its antibacterial properties. The leaf extract was tested against gram-negative, gram-positive bacterial, and fungal strains; the zone of inhibition was measured. The standard drugs used were ampicillin and itraconazole. The methanolic extract has shown the highest activity against *Staphylococcus aureus* at mild concentrations compared to *Escherichia coli* (Edupuganti et al., 2015). *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus,* and *Bacillus subtilis* were tested against solvent extracts of *A. indicum* cultured in Muller Hinton agar medium. Results concluded that the leaf extract of this plant showed higher activity against *Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus,* and *Escherichia coli* (25, 18, 25, and 17 mm). Moderate effects were shown in CE for all the bacteria except *Klebsiella pneumoniae*. No effects were seen in the aqueous extract for all the organisms tested (Poonkothai, 2006). In an experiment, 16 microbial strains (gram-positive and gram-negative bacteria and fungi) were tested. Crude and methanolic extracts of *Abutilon indicum* were tested against 16 strains, and brine shrimp lethality bioassay was used to detect cytotoxic effects. Results concluded that carbon tetrachloride produced an average zone of inhibition of 7–10 mm at a concentration of 400 µg/disc. No bacterial activity is seen in CE except *Sarcina lutea*. Promising cytotoxicity is produced by the plant's chloroform portion of methanolic extract (Abdul et al., 2010).

46.3.7 ANTI-INFLAMMATORY ACTIVITY

Abutilon indicum plants were extracted with petroleum and ethanol; for the study, 30 rats were selected and induced edema by injecting carrageenan into the paw, which causes inflammation (edema). This inflammation of

the paw was measured using the plethysmographic meter before and after the induction of edema. Diclofenac was the standard drug for this study. The remaining groups were administered with *Abutilon indicum* extracts of aqueous, ethanolic, and chloroform. The result confers that the EE of *Abutilon indicum (*of 400 mg/kg bw*)* showed promising results by reducing inflammation comparable to the standard drug (35 to 37 mg/kg bw) after 4 hrs. of treatment (Saraswathi et al., 2011). Another experiment proves the anti-inflammatory activity of *A. indicum. Abutilon indicum* extract with doses 250, 500, and 750 mg/kg was used in albino rats, and dermally carrageenan was injected into rat paws, which induces inflammation. After 3 hours of analysis, the result showed a high inhibition percentage of around 65% edema on 750 mg/kg of dose level of *A. indicum* plant extracts (Tripathi et al., 2012).

46.3.8 ANALGESIC ACTIVITY

Roots of *Abutilon indicum* are collected and air-dried in the shade to make a fine powdery form. The ethanol, methanol, and aqueous extract were used. Adult Swiss albino mice were tested against the *A. indicum* extracts. Analgesic activity was identified by the writhing method, tail immersion, and tail-flick method. Doses of extracts were given to the rats accordingly. Gum acacia solution was used as a control group. Results showed maximum inhibition was due to petroleum ether extract followed by the aqueous and EE. However, methanol extract (ME) did not produce any changes in analgesic rats. The effect of petroleum ether extract was similar to that of aspirin (Goyal et al., 2009).

46.3.9 ANTIHELMINTHIC ACTIVITY

The intestinal worms compete for the nutrients and minerals of humans and animals. The affected individuals became anemic, so several studies were undertaken to treat and kill the intestinal worms. Sheep tapeworms *Moniezia expansa* were exposed to *A. indicum* extracts to analyze the antihelminthic activity with different doses viz, 25, 50, and 100 mg/ml. Worms were taken in different plates; one was treated with 10 mg/ml albendazole, a standard drug, and negative control. The remaining worms in plates were administered with different doses of *Abutilon indicum* extract. After 1–2 hrs. of observation, the paralysis and death time of worms were calculated. The results showed

that 100 mg/ml of *Abutilon indicum* plant extract showed good mortality and paralysis in less time, which is better than the standard drug (Thooyavan et al., 2018). In another experiment, the study used *A. indicum* leaf extracts with ethyl acetate (EAE), aqueous, and carbon tetrachloride fraction against earthworm *Pheretima posthuma*. The earthworms were taken in different plates; each plate was administered with normal saline, albendazole, alcoholic extract of *Abutilon indicum*, and carbon tetrachloride extracted with *Abutilon indicum*. The result showed that the paralysis time for alcoholic extract is 13–14 min for mortality is 19–20 min, which is very near the standard albendazole drug. It showed 11–12 min for paralysis and 15–16 min for mortality. These studies prove the antihelminthic activity of *A. indicum* extracts (Ranjit et al., 2013).

KEYWORDS

- ***Abutilon indicum***
- **anti-asthmatic activity**
- **antidiabetic activity**
- **gastric ulcer index**
- **Indian mallow**
- **proliferator-activated receptor**

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CHAPTER 47

Acalypha australis L.: Bioactive Potential and Pharmacological Activities

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47.1 INTRODUCTION

Acalypha australis L. is called Asian copperleaf. It grows in humid plains in maximum parts of Asia and is one of the potherbs widespread among Asian inhabitants. It is a dicot plant belonging to the Euphorbiaceae family that grows wildly on the roadside, grass, and mountain slope. Except for Neil Mongol and Xinjiang, *Acalypha austalis* cover all parts of China, parts of Japan, Korea, Laos, the Philippines, Eastern Russia, and Vietnam. It is also present in New York (Delendick, 1990), North Australia, Queensland, Victoria, and Eastern India (Atlas of Living Australia, 2013; Singh, 1967). It is an herbaceous annual plant with 20–30 cm tall with oblong to lanceolate leaves. The plant has per bract 1–3 female flowers (3 sepals), and 5–7 male flowers (4 sepals) that develop in an auxiliary panicle with 15–50 cm long inflorescence.

The combined effect of *Acalypha australis* with berberine is mainly the content of Xiancai Huangliansu Capsule that is used for the treatment of diarrhea (Lei-Lei, 2013). They reported that *Acalypha australis* is rich in flavonoids (Cui et al., 2013). It is used for the treatment of diarrhea and snakebite in China as a traditional herbal medicine. *Acalypha australis* is

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used to cure dysentery, diarrhea (Deng and Hu, 2005), scrofula, dermatitis, nosebleed, hemoptysis, cough relieving (Li et al., 2009) and to cure swollen feet (You et al., 2021). The leaves are used in poulticing snake bites.

47.2 BIOACTIVE COMPOUNDS

Acalypha australis has several bioactive compounds such as Emodin, beta-sitosterol, 2,6-dimethoxy-1,4-benzoquinone, nicotinic acid, protocatechuic acid, daucosterol, gallic acid, succinic acid, brevifolin, (+)-catechin, (–)-epicatechin, gallocatechin, epigallocatechin (EGC), chlorogenic acid, quercetin, rutin, gallic acid, and *p*-hydroxybenzaldehyde (Wang et al., 2008). The structures of each bioactive compound are given in Figures 47.1 and 47.2. *Acalypha australis* has three active compounds that show significantly ameliorating ulcerative colitis, including 4-hydroxybenzoic acid methyl ester, 3-methoxy-4-hydroxybenzoic acid, and protocatechuic acid (Deng et al., 2007).

47.3 PHARMACOLOGICAL ACTIVITIES

47.3.1 ANTI-INFLAMMATORY ACTIVITY

Acalypha australis (AAL) was investigated for its anti-inflammatory effect. The various inflammatory mediates like cytokines, nitric oxide (NO), and other chemicals which are released from pro-inflammatory cells, such as macrophages, act as an inflammatory molecules (Kim et al., 2017). AAL inhibits iNOS expression and IL-6 and interleukin-1β (IL-1β) production in LPS-induced septic mice. In addition, it reduces the expression of NF-κB-related proteins. It was found that the AAL reduced the production of NO in the macrophages-induced model (Kim et al., 2020).

47.3.2 ANTIBACTERIAL ACTIVITY

The recent investigation showed that the AAL constitutes various compounds such as (+)-catechin, (–)-epicatechin, gallocatechin, EGC, chlorogenic acid, quercetin, rutin, gallic acid, and *p*-hydroxybenzaldehyde (Siems et al., 1996; Reiersen et al., 2003). On the basis of HPLC analysis, it was found that

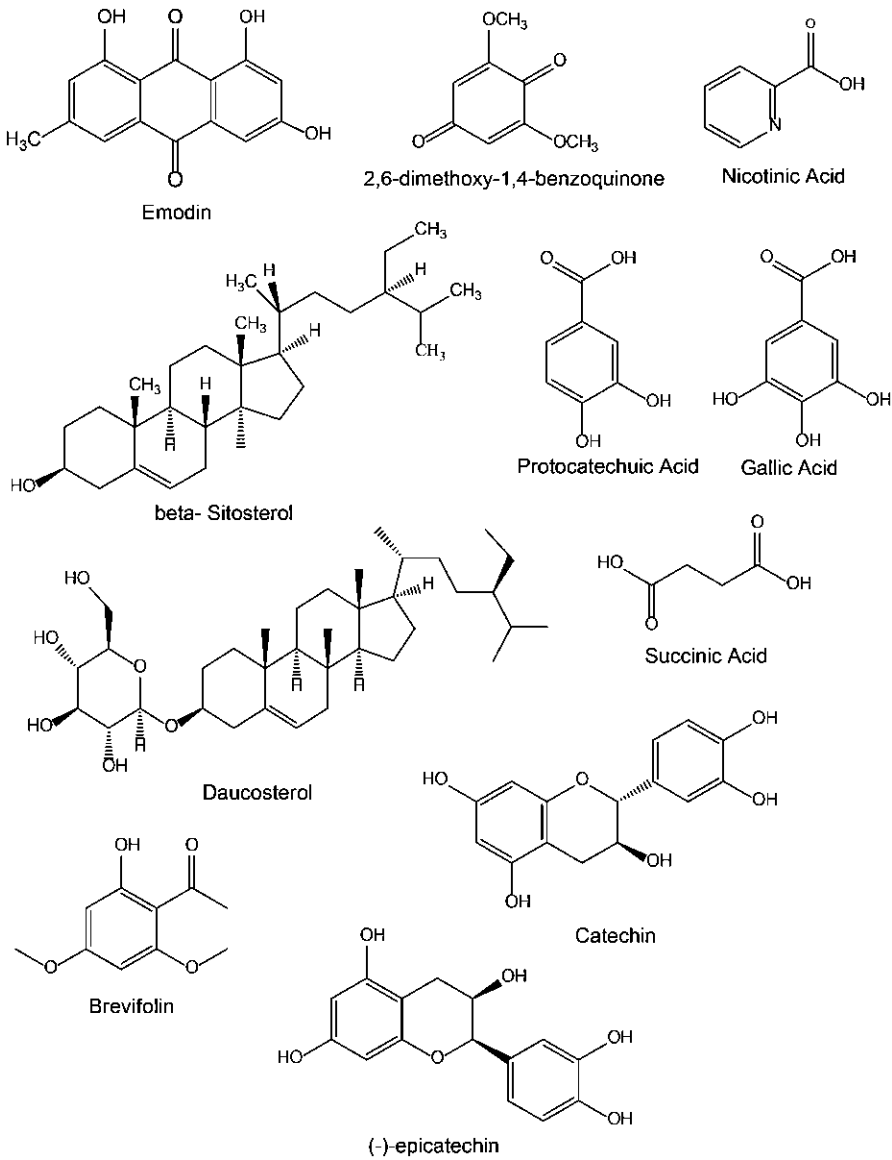


FIGURE 47.1 Structure of bioactive compounds of *Acalypha australis* L.

the gallic acid and other compounds having molecular weight 634.1 contain antibacterial activity, and both the compounds increase the antibacterial efficiency of crude extract of AAL by 10 to 20 times (Xiao et al., 2013). Kirby-Bauer disc diffusion method used for *in vitro* studies of above chemical

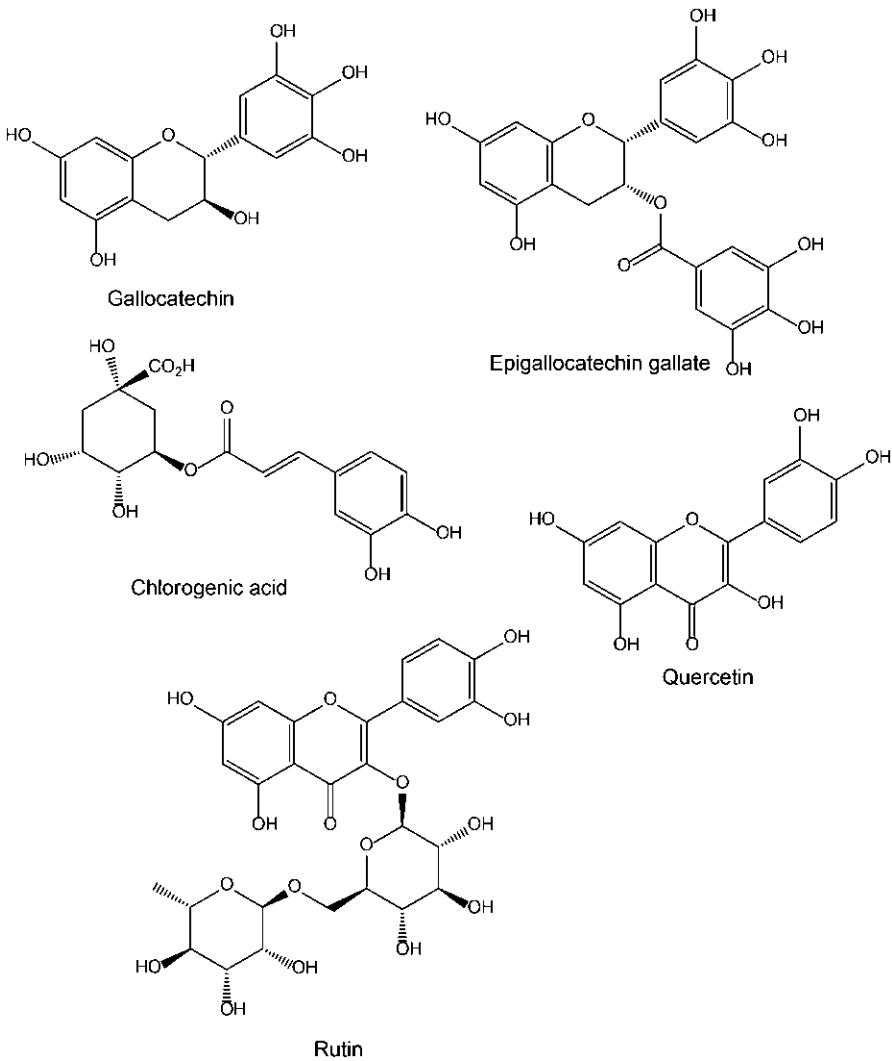


FIGURE 47.2 Some more bioactive compounds of *Acalypha australis* L.

compound found in AAL (Drew et al., 1972). Broth dilution method is used to determine the MIC value against the gram-positive and gram-negative bacteria of different strains (Wiegand et al., 2008). Both bacteria were grown by using the nutrient agar media and incubated at 37°C for 48 h. Dimethyl sulfoxide is used as a solvent for the above compound. The compound quercetin, (+) (–) catechin, and rutin exhibit medium antibacterial activity

against *B. subtilis*, *S. aureus*, *E. coli*, and *S. typhiuriun*, and compounds p-hydroxybenzaldehyde, (–)-epicatechin, gallocatechin, EGC, chlorogenic acid exhibit potent activity against *B. subtilis*, *S. aureus*, and *E. coli* (Fan et al., 2012).

47.3.3 APOPTOTIC ACTIVITY

A cell proliferation assay kit (Cell Titer 96 Aqueous One Solution, Promega) is used to determine the impact of *Acalypha australis* (MEAL) and *Dianthus chinensis* (MEDC) on cell viability. Cells were grown in 96-well plates and then incubated with different doses of MEDC and MEAL at different time periods. By using enzyme-linked immunosorbent assay (ELISA) absorbance was recorded at 490 nm. Because Sp1 is a good target for mouth cancer, four natural products were investigated to determine whether they can simultaneously decrease Sp1 protein expression, inhibit cell growth, and induce apoptosis in SCC-15 and YD-15 cells. MEDC, MEAL, methanol extract (ME) of *I. balsamina* (MEIB) and methramycin A significantly inhibited the cell viability of both cell lines, whereas ME of *Pteridium aquilinium* (MEPA) did not inhibit. The effects of these natural products on Sp1 expression and PARP cleavage further investigation were done and found MEDC and MEAL-treated cells showed reduced expression of Sp1, and increased PARP cleavage compared to cells treated with vehicle control. MEIB-induced PARP cleavage, did not have a significant effect on Sp1 protein levels. These results indicated that both MEDC and MEAL have antiproliferative and apoptotic effects and inhibit Sp1 protein expression in human oral cancer cells (Shin et al., 2012).

47.3.4 ANTI-DIABETIC EFFECT

To determine the antidiabetic activity of the extract of AAL study was performed on streptozotocin (STZ) induced high blood glucose levels in Balb/c mice. In this study, 16 male mice were used as experimental animals aged 4–6 weeks and weight 20–30 grams. Mice were divided into two groups and observed for GDC levels after 14 days of treatment, and it concluded that the herbal extract of AAL reduced the high glucose level in mice induced by STZ as same as metformin (Ocktarini et al., 2011).

47.3.5 ANTI-CHOLESTEROL EFFECT

The anticholesterol activity was investigated of water extract of AAL on a high-fat diet (HFD) induced male mice. This study was conducted with 36 9-week-old mice, and these were divided into a control group (6 mice) and HFD group (30 mice). After 12 weeks, HFD group mice were further divided into the model (saline, 6 mL/kg), simvastatin (0.11 mg/mL, 6 mL/kg), and AAL treatment (low, middle, and high dosage: 300, 600, and 900 mg/kg) group, with 6 animals per group. The water extract of AAL significantly reduced serum cholesterol, triglyceride, and LDL-C and increased HDL-C levels and leading to reduced gained body weight, fat pad weight, and Lee's index in obese mice (You et al., 2021).

47.3.6 HEPATOPROTECTIVE ACTIVITY

AAL showed a hepatoprotective effect against HFD-induced liver toxicity. The result data showed that administration of HFD in mice causes increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels that indicate HFD-induced liver toxicity. These liver function parameters were significantly decreased by the administration of AAL. Therefore, it was concluded AAL has hepatoprotective active (You et al., 2021).

KEYWORDS

- ***Acalypha australis***
- **alanine aminotransferase**
- **aspartate aminotransferase**
- **enzyme-linked immunosorbent assay**
- **interleukin-1β**
- **methanol extract**

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CHAPTER 48

Bioactives and Pharmacology of *Acalypha wilkesiana* Müll.-Arg.

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48.1 INTRODUCTION

Acalypha wilkesiana Müll.-Arg. (Syn.: *Acalypha tricolor* Seem.) (Family: Euphorbiaceae) is an herb cropping up to a height of 300 cm (9.8 ft). Stem and branches are organized closely like a crown. Fine hair-like structures is observed on both the leaves and branches. The leaves of this plant are broad, large, variegated, and multi-colored. Leaves are in coppery green with yellow (or) red splashes, which utter them a mottled appearance. This plant contains both male and female flowers on the same plant. Basically, male flowers are with long spikes up to 12 cm, and female flowers are with short spikes. *A. wilkesiana* is an herb cultivated all around the world in the tropical areas of America, Africa, and Asia. The plant is distributed in Botswana, Bermuda, Brazil, Thailand, Uganda, and Vietnam. The leaves of *A. wilkesiana* are used for the treatment of fungal infections, gastrointestinal disorders, and liver

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toxicity (Oyelami et al., 2003; Olukunle et al., 2015). Leaves of this plant are eaten like a vegetable for the treatment of hypertension (Ikewuchi et al., 2008). Vernacular names of *A. wilkesiana* are beefsteak plant, Match-Me-If-You-Can, Joseph's coat, red leaf, and Fire Dragon plant.

A. wilkesiana leaves are extensively used in Ayurvedic treatment in the form of juice (squeezed from the leaves) for the treatment of diarrhea, dysentery, laryngitis, ruptured appendix, fevers, and in bacterial, fungal infections (Westphal et al., 1986; World Health Organization, 2009). It is documented that leaves combined with bark is drunk to treat pleurisy (Westphal et al., 1986).

48.2 BIOACTIVES

Methanolic extracts of *A. wilkesiana* leaves, root bark, and stem bark revealed the presence of terpenoids, saponins, alkaloids, flavonoids, anthraquinones, glycosides, tannins, and steroids (Oladunmoye, 2006; Igwe et al., 2016) terpenes, fatty acyl alcohols with long-chain, esters, phytol acetate, phytol, sterols like sitosterol, campesterol, stigmasterol, and Vitamin E. Additionally constituents like sesquiterpenes, monoterpenes, triterpenoids, and polyphenols are revealed in the plant *A. wilkesiana* (Akinde, 1986). Among the bioactive constituents, the most important constituents from *A. wilkesiana* are flavonoids, tannins, alkaloids, and phenolic compounds (Dabai et al., 2013).

Recent studies revealed that EE of various parts of *A. wilkesiana* contains tetradecanoic acid, octadecanoic acid, xanthone, octadecanoic acid methyl ester, stigmasterol with the help of GC-MS analysis (Oyabode et al., 2018). Phytol acetate is the active constituent isolated from EE of the leaves of the plant by using n-hexane, ethyl acetate (EAE) and ethanol. Similarly, constituents like sitosterol, acridin-9-yl-(4-methoxy-phenyl)-amine, oleana-11,13 (18)-diene, campesterol also extracted from leaves of *A. wilkesiana* (Oyabode et al., 2018). Hexadecanoic acid methyl ester, stigmasterol, 9-(4-methoxy phenyl) xanthene is extracted from the root bark of the plant by GS-MS (Oyabode et al., 2018).

During the quantitative analysis of constituents of *A. wilkesiana*, it is proved that aqueous extract contains saponins in highest amount. The ethanol extract contains phenols, steroids, tannins, and terpenoids in highest amount (Sofowora, 1993). Shikimic acid is reported as a major constituent of the plant (Anokwuru et al., 2014).

From the recent GC-MS analysis of the plant, bioactive constituents like 3-methylene-1-vinyl-1-cyclopentene, 2-vinylbicyclo [2.1.1] hex-2-ene,

butane-1,4-diol, acrylic acid butyl ester, acetophenone, palmitic acid, 1,4-dimethylbenzene, 2-butenyl propionate, styryl alcohol, 2-ethyl-hexene, and phenylethyl alcohol are isolated (Igwe et al., 2016).

The structures of compounds present in *A. wilkesiana* are depicted in Figures 48.1 and 48.2.

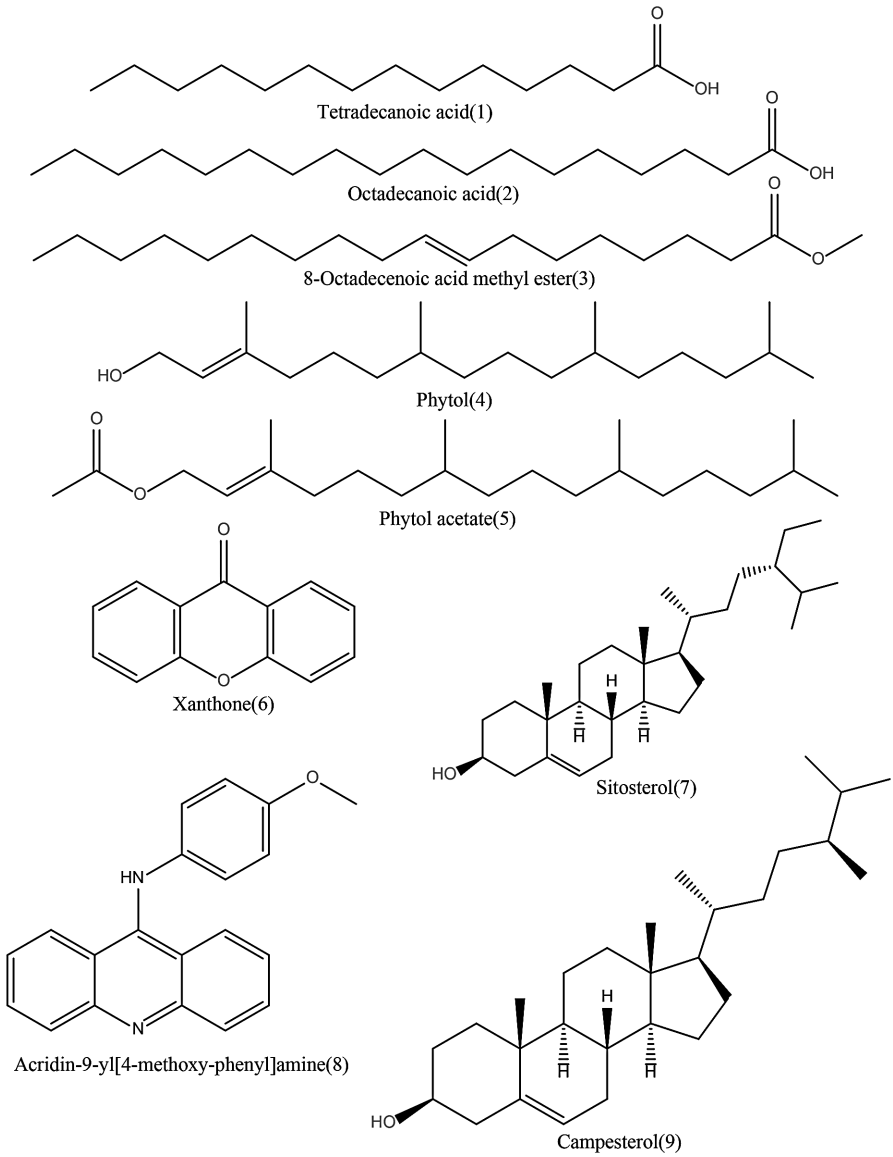


FIGURE 48.1 Structures of the phytoconstituents (1–9) of *Acalypha wilkesiana*.

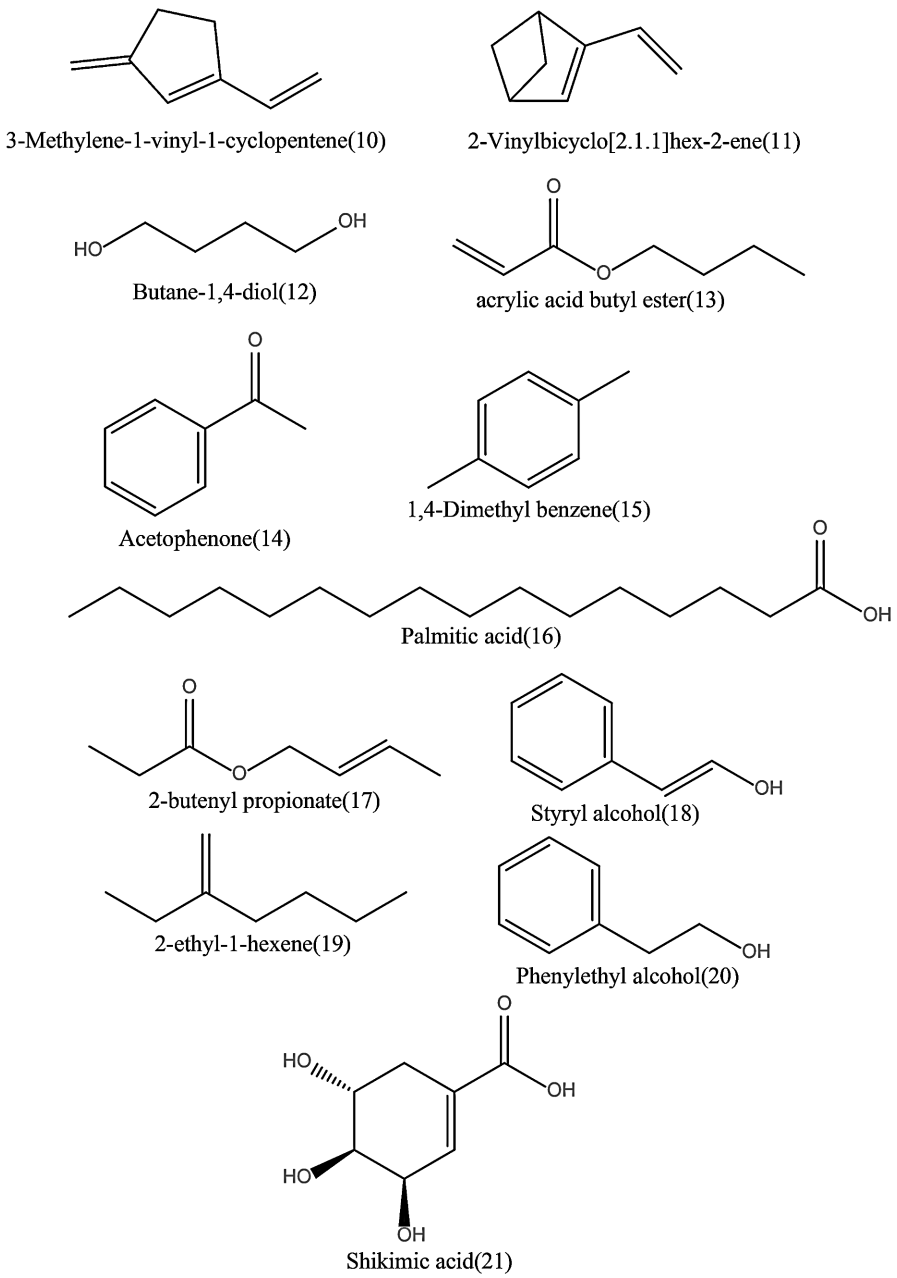


FIGURE 48.2 Structures of the phytoconstituents (10–21) of *Acalypha wilkesiana*.

48.3 PHARMACOLOGY

48.3.1 ANTI-DIABETIC ACTIVITY

A. wilkesiana EEs of stem bark, leaves, and root bark were undergone for GC-MS analysis to know the bioactive compounds which produce inhibitory activities on two enzymes called α-glucosidase and α-amylase, which play a key role in diabetes. Studies proved that EE of root bark exhibited the most effective inhibitory activity against pancreatic α-amylase with the lowest EC_{50} value of 6.25 ± 1.05 μg mL^{-1} when compared with other plant parts (Oyabode et al., 2018).

48.3.2 ANTIBACTERIAL ACTIVITY

Phytochemical screening confirmed that saponins, phenols, flavonoids, and triterpenes are extracted from *A. wilkesiana,* and these bioactive constituents combined with silver are responsible for antibacterial activity against both gram-positive and gram-negative bacteria (Dada et al., 2019). Geranin is a bioactive isolated from *A. wilkesiana* and showed antibacterial activity by inhibiting the growth of *S. aureus* (Anokwuru et al., 2014). Corilagin is a compound extracted and showed growth inhibition of *Escherichia coli*. Both EAE and ethanol extract of *A. wilkesiana* showed inhibition against gram-negative *E. coli*. Ethanol extract showed maximum inhibition of bacteria (Anokwuru et al., 2014).

48.3.3 ANTIOXIDANT ACTIVITY

Antioxidant activity was exhibited by the bioactive compound corilagin isolated from *A. wilkesiana* by using organic solvents (Anokwuru et al., 2014).

48.3.4 APOPTOSIS

Previous studies proved that the EAE and hexane extracts of the plant contain maximum cytotoxic effects that activate apoptosis in DNA SSBs and DSBs-induced U87MG and A549 cancer cells (Lim et al., 2011). EEs of *A. wilkesiana* seeds showed apoptosis-inducing property, which is measured by the cytokines release and function of granulocyte (Büssing et al., 1999).

EAE extract of the plant showed a good antiproliferative effect against both A549 and U87MG cells with GI_{50} = 89.63 ± 2.12 μg/ml and GI_{50} = 28.03 ± 6.44 μg/ml. Another extract with hexane of the plant exhibited effective

antiproliferative effects on U87MG (GI_{50} = 166.30 ± 30.50 μg/ml) (Lim et al., 2011).

48.3.5 ANTI-PLASMODIAL ACTIVITY

Crude aqueous ME of the plant was tested for anti-plasmodial activity against the parasites of *Plasmodium falciparum* 3D7 strain by performing the SYBR Green assay. Results showed the possibility of novel malarial drugs from the plant (Amlabu et al., 2018).

48.3.6 ANTI-INFLAMMATORY ACTIVITY

Polyphenol fractions extracted from leaves of *A. wilkesiana* experiment with anti-inflammatory activity on LPS-stimulated RAW 264.7 macrophages and acetaminophen-induced liver injury mouse model. It is proved that polyphenol fraction reduced the proinflammatory cytokines secretion and tumor necrosis factor (TNF)-α-in LPS-stimulated RAW 264.7 macrophages (Wu et al., 2018).

48.3.7 ANTI-ATHEROSCLEROTIC ACTIVITY

Palmitic acid or n-hexadecanoic acid, which is extracted from *A. wilkesiana* with a retention time of 19.935 and 20.92% of peak area, showed mild anti-atherosclerotic activity (Cho, 2015).

KEYWORDS

- ***Acalypha wilkesiana***
- **anti-inflammatory activity**
- **apoptosis**
- **bioactives**
- **palmitic acid**
- **pharmacology**

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CHAPTER 49

Pharmacological Aspects of Underutilized Plant *Bridelia stipularis* (L.) Blume

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49.1 INTRODUCTION

Bridelia comprises approximately 60–70 species from Asia to Africa. *Bridelia stipularis* (L.) Blume, a perennial evergreen woody climber or scandent shrub, belongs to the family Euphorbiaceae and is distributed in the warm regions of India. This species is native to the Indian subcontinent to Southeast Asia and widely distributed across the world. The currently accepted name for this plant is *Bridelia stipularis* (L.) Blume as per the Kew Plant List. There are several synonyms of the plant, one of them being *Bridelia scandens* (Roxb.) Willd.

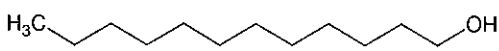
Bridelia is an evergreen large shrub. Leaves leathery, elliptic-obovate or orbicular-oblong. Flowers are in axillary clusters with long stipular bracts. Male flowers are very short. Cup-shaped receptacle; sepals are ovate-triangular while petals are spoon-shaped. Fruits are oblong in shape, sitting on calyx.

Bridelia stipularis is used for the treatment of cough, fever, and asthma (Rajkumar and Rajanna, 2011). Furthermore, the leaf extracts are used to treatment of jaundice (Jose et al., 2011; Lalitha Rani et al., 2011) and allergy (Rahman, 2010; Khisha et al., 2012). Khai-phid-nam is a kind of fever in the Thai language. On the basis of healers' information *Bridelia stipularis* was being used for the treatment of this fever (Oratai et al., 2012).

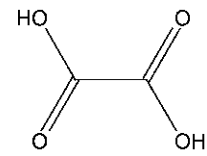
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49.2 BIOACTIVES

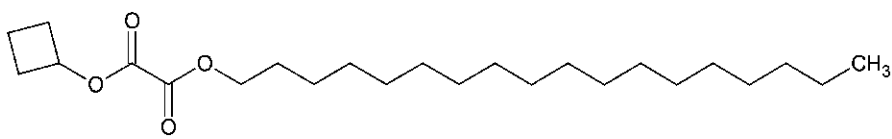
Various phytochemicals were isolated by a number of workers from the different parts of the *Bridelia stipularis.* Three compounds afforded from the stem bark (methanolic extracts) of *B. stipularis,* which were identified as glut-5(6)-en-3-one (1), glut-5(6)-en-3α-ol (2), and (22E)-7-hydroxy-28-methylcholesta-4,22-dien-3-one (3). These three compounds showed activities against fungi and bacteria (Anjum et al., 2016). Yusufzai, in 2019 extracted stem of *Bridelia stipularis* for detailed chemical profiling and showed 1-dodecanol, oxalic acid, cyclobutyl octadecyl ester, 1-octanol, 2-nitro, benzaldehyde, 2,4-dimethyl-, 4-tridecanol (6.359%) and nonyl ester (5.616%) as major components. *Bridelia stipularis* leaves revealed with three major flavonoids, named as apigenin, 7-O-methyl luteolin and 5,7,2′,5′-tetrahydroxyflavone for the first time from this plant (Puja et al., 2020). Sengupta and Ghosh, in 1963 isolated fatty alcohol, $C_{22}H_{46}O$, named bridelyl alcohol, besides fatty acids and a phlobatannin from the leaves of *Bridelia stipularis*. Taraxenone compound was isolated from roots of *Bridelia stipularis* (Desai et al., 1976).



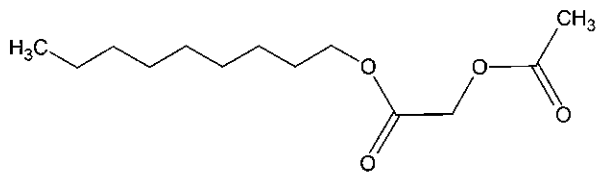
1-dodecanol



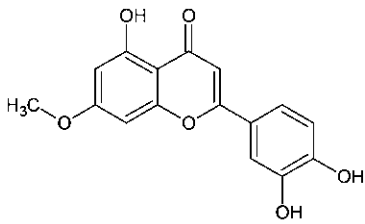
Oxalic acid



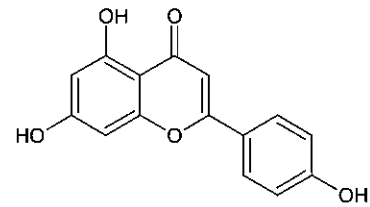
Cyclobutyl octadecyl ester.



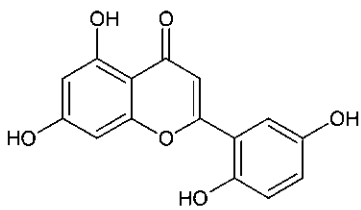
Nonyl ester



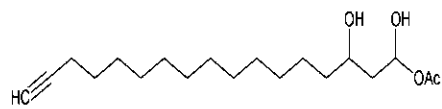
7-O-methyl luteolin or7-O-methylluteolin



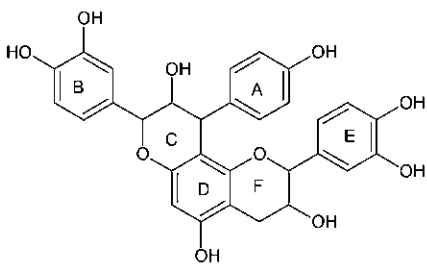
Apigenin



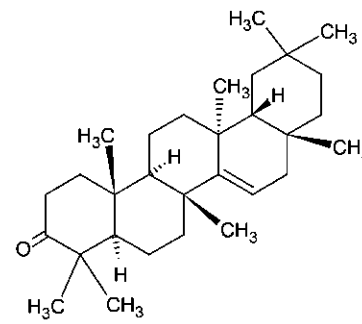
5, 7, 2', 5' tetrahydroxyflavone



Fatty alcohol



Phlobatannin



Taraxenone

49.3 PHARMACOLOGY

49.3.1 ANTIBACTERIAL ACTIVITY

Bridelia stipularis leaves showed significant activities against *Streptococcus mutans, Streptococcus mitis, Streptococcus salivarius,* and *Lactobacillus acidophilus* (Mallya et al., 2018). *B. stipularis* leaves also showed potential antibacterial activities (showed mild to strong activity with zone of inhibition between the ranges of 11.9 to 23.0 mm) against 13 different species of bacteria (*Bacillus cereus, Sarcina lutea, B. megaterium, B. subtilis, Escherichia coli, Staphylococcus aureus, Salmonella paratyphi, Pseudomonas*

aeruginosa, S. typhi, Shigella boydii, S. dysenteriae, Vibro meniscus, V. parahemolyticus) due to the chemical constituents which have a casual role in the *in vivo* prevention of bacterial diseases (Anjum et al., 2011).

49.3.2 THROMBOLYTIC ACTIVITY

Methanolic plant extract of *B. stipularis* showed promising thrombolytic activity compared to the clot lysis percentage attained through streptokinase. The phytochemicals of *B. stipularis* could be used as a thrombolytic agent for the progress of patients suffering from coronary atherothrombotic diseases (Biozid et al., 2015). The extract of *B. stipularis* indicated potential sources of cardio-protective drugs, which need to be isolated and characterize for further details (Anjum et al., 2013).

49.3.3 ANTIFUNGAL ACTIVITY

The aqueous extract of *B. stipularis* dried leaves is effective against more than 4 *Candida* species, this extract controls for 80% of oral lesions caused by it (Mallya et al., 2015). The leaf extract of *Bridelia stipularis* showed that plants possess some chemical components which act against the fungi *Candida albicans* (Mallya et al., 2018). Four different solvents of leaf extracts of *B. stipularis* showed significant antifungal activity against *Aspergillus niger, Candida albicans*, and *Saccharomyces cerevisiae* (Anjum et al., 2011).

49.3.4 ANTIOXIDANT EFFICACY

B. stipularis stem showed potential antioxidant properties by using different solvents like hexane, chloroform, and ethyl acetate (EAE) (Yusufzai et al., 2019). The obtained results indicated that extract of *B. stipularis* have the potential sources of natural antioxidants, which needs to be isolated and characterize the compounds for further work (Anjum et al., 2013). Three flavonoids isolated from the leaves of *B. stipularis* viz. 7-O-methyl luteolin, apigenin, and 5,7,2′,5′-tetrahydroxyflavone showed antioxidant activity (Puja et al., 2020). The methanolic extract of *B. stipulrais* showed strongest antioxidant activity as compared to the EAE and petroleum ether extracts, because of higher contents of tannins, phenolic, flavonoids, and saponoins (Senthilkumar et al., 2010). High content of flavonoids found in the methanolic extract of *B. stipularis* involved in antioxidant activity (Senthilkumar et al., 2010). Ethanol extract of *B. stipulris* showed good scavenging and

reducing capacity due to phytoconstituents like phenols, flavonoids, tannins, and alkaloids present in it (Jinadatta et al., 2017).

49.3.5 HYPOGLYCEMIC ACTIVITY

B. stipularis leaf extract significantly depleted the total cholesterol (TC) concentration in treated STZ-induced diabetic rats, which could be beneficial in preventing diabetic complications (Neethu et al., 2015).

49.3.6 ANTIDIABETIC PROPERTIES

Treatment of alloxan-induced diabetic rats, with the alcoholic extract of *B. stipularis*, can be successfully utilized for the management of diabetes (Khan et al., 2018).

49.4 CONCLUSION

The present literature available confirms no toxicity of compounds reported from *Bridelia stipularis*. Furthermore, there is a need to be clinical trials and the determination of the stability and toxicity of isolated chemical compounds. Information collected in this review shows that instead of many phytochemicals recorded, *Bridelia stipularis* have not been fully explored. Some applications in pharmacological views are mentioned here, but further investigations on phytochemicals, their screening, and applications are needed for opening new opportunities.

KEYWORDS

- **antidiabetic properties**
- ***Bridelia stipularis***
- **Euphorbiaceae**
- **nephroprotective actions**
- **phytochemicals**
- **streptozotocin**
- **thrombolytic activity**

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CHAPTER 50

Phytochemical and Pharmacological profile of *Euphorbia antiquorum* L. (Euphorbiaceae)

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50.1 INTRODUCTION

Euphorbia antiquorum L. (family Euphorbiaceae) is a succulent plant. *E. antiquorum* has good medicinal properties. The juice is used as an anti-inflammatory, purgative, rheumatism, dropsy, gout, neuropathy, deafness, cough, and cutaneous infections (Jyothi et al., 2008).

E. antiquorum plants are trees, up to 10 m tall; stems woody, terete; branches jointed, 3-winged, spreading; wings broad, wavy-margined; podaria in rows, 1.5–2 cm apart, slightly lobulate; spines 2, divaricate. Leaves sessile, broadly ovate or sub-orbicular, obtuse at base, entire, apiculate at apex, 5–12×3–6 mm, fleshy, glabrous, early caducous. Cyathia in simple axillary dichasial cymes, central one sessile, lateral two pedunculate; bracts broadly triangular, obtuse; involucres turbinate, pinkish outside; lobes 5, 3 mm in diam., laciniate; glands 5, transversely oblong, fleshy. *Male florets*: in 5 fascicles of 5 or 6 flowers each; bracteoles broadly setaceous, deeply laciniate, 3 mm long, overtopping anthers. *Female floret*: gynophores ca 2 mm long; ovary ca 4 mm in diam. Fruits trilobed, 7–9 mm in diameter obtusely keeled, separating into 3 bivalved, 1-seeded cocci, yellowish orange; seeds globose, 3 mm in diam., grayish brown.

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50.2 BIOACTIVES

E. antiquorum contains triterpenes, diterpenes, and flavonoids such as the lathyrane, jatrophane, ingenane, tigliane, ingol, and myrsinol types, few diterpenoids showed antimicrobial, cytotoxic anti-HIV and anti-inflammatory activities. It also contains euphol, antiquol A, antiquorin, euphorbol, isohelinol, and camelliol. *E. antiquorum* which is used in traditional medicines in treating various diseases including waxy growths, warts, skin cancer, corns, catarrh, and asthma also contains Ingenol 3-angelate (Noemi et al., 2004). Latex of the plant EA contains, 10alpha-eupha-5, 9(11), 24-trien-3beta-ol (antiquol C), eupha-7,19(10→9) abeo-8alpha, 9beta, 24-dien-3beta-ol (antiquol B), and 24(24(1))-dien-3beta-ol (euphorbol), 24-methyltirucalla-8, lemmaphylla-7, 21-dien-3beta-ol, isohelianol, and camelliol C showed potential inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) activation induced by the tumor promoter 12-O-etradecanoylphorbol-13-acetate (TPA) Akihisa et al. (2002). From *E. antiquorum* stem three new triterpenoids, were isolated namely 30-diol diacetate, 30-acetoxyfriedelan-3β-ol, friedelane-3β, and 3β-acetoxyfriedelan-30-ol (Anjaneyulu and Ravi, 1989). From the latex of ethyl acetate (EAE) extract, three new triterpenes, antiquol A, Euphol 3-O-cinnamate, and antiquol B, along with known triterpenes, cycloeucalenol, euphol, 24-methylenecycloartanol and, sitosterol, (Z)-9-nonacosene, and p-acetoxyphenol have been isolated from the *E. antiquorum* latex (Gewali et al., 1990). *E. antiquorum* also contains epi-friedelanol and taraxerolin the stembark, taraxerol, friedelan-3β-ol and 3α-ol, and taraxerone in the stems, cycloartenol, β-amyrin, and ingenol type diterpenoids found in the latex. Around 18 new euphorantins A-R (1–18) and ingol-type diterpenes have been reported in the latex (Anjaneyulu and Ravi, 1989; Gewali et al., 1990).

50.3 PHARMACOLOGICAL ACTIVITIES

50.3.1 CYTOTOXIC ACTIVITY

Cytotoxic effects of *E. antiquorum* latex against *Saccharomyces cerevisiae* cells were analyzed using neutral red, MTT, SRB. Five different concentrations of latex extract, i.e., 50, 40, 30, 20, 10 g has been tested for cytotoxicity. The results showed that compared to higher concentration, the latex of lower-concentration cells showed better survival (Sumathi et al., 2011a).

The latex of *E. antiquorum* showed significant inhibition on different cancer cell lines. Morphological changes have been observed due to EA latex-induced apoptosis. EA suppressed the Bcl-2 expression, reduced cleavage of Bid, increased bax and the tranlocation of t-Bid to the mitochondria and release of cytochrome C. EA caused increased cellular reactive oxygen species (ROS). Induced ROS formation suppressed by allopurinol or cyclosporine, it also increased expression of FasL, Fas, and c-Jun N-terminal Kinase (JNK), mitogen-activated protein kinase (MAPK) and P38 decreased expression of the extracellular signal-regulated kinase (ERK) in human cervical adenocarcinoma HeLa cells (Wen et al., 2012).

50.3.2 HEPATOPROTECTIVE AND ANTIOXIDANT ACTIVITY

Jyothi et al. (2008) reported the hepatoprotective and antioxidant activity of *E. antiquorum.* In the groups treated with 125 mg/kg and 250 mg/kg of the (EA) extract, the biochemical markers of hepatotoxicity were decreased when compared to CCl_4 treated control group. The hepatoprotective effects of a higher dose of EA (250 mg/kg) were near to that of standard, i.e., Silymarin (100 mg/kg). Both doses of EA showed more significant hepatoprotective properties than the control.

The absorbance at 560 nm with EA indicates the consumption of superoxide anion radical in the reaction mixture. About 100 µg of the sample possesses 73% of inhibition as compared to the standard sodium metabisulfite (25 µg), which showed 86% inhibition/scavenging activity reported by Jyothi et al. (2008).

50.3.3 ANTI-HYPERGLYCEMIC ACTIVITY

The aqueous and alcoholic extract of *E. antiquorum* root extract has been tested for hyperglycemic activity on streptozotocin (STZ)-nicotinamide-induced and fructose-induced rats. The diabetic rats induced with alloxan were treated with 200 mg/kg of pet. ether, alcohol, and water extracts (WEs) of *E. antiquorum.* The ethanol extract of *E. antiquorum* root exhibited a significant reduction in blood sugar level after 1 hour post-treatment (30.11%). The results revealed that all the EA extracts of *E. antiquorum* have a hypoglycemic effect. The ethanol extract showed a significant hypoglycemic effect of 69% compared to the standard drug Glibenclamide. Antiquol A is the best aldose reductase inhibitor with Glide score – 9.07 Kcal/mol (Amuth et al., 2012; Madhavan et al., 2015).

50.3.4 ANTI-INFLAMMATORY AND ANTI-ARTHRITIC ACTIVITIES

The arthritic potential and anti-inflammatory activity have been evaluated with and alcoholic (EEA), aqueous (AEA) extracts of EA. The potentiality of the extracts was evaluated by using acute inflammation and chronic inflammation arthritis in rats. In acute oral toxicity study, AEA, and EEA did not report toxicity and mortality up to the dose of 2 g/kg. EEA and AEA at 400 and 200 mg/kg, po showed significant inhibition of carrageenan-induced rat paw edema. EEA and AEA at 400 mg/kg, showed good inhibition of cotton pellet-induced granuloma formation in rats. Triterpenoids in the extracts of EA might be responsible for anti-arthritic effects and anti-inflammatory (Anand et al., 2011).

50.3.5 ANTIMICROBIAL ACTIVITY

E. antiquorum latex extract was used for to determine the antimicrobial activity by disc diffusion method, against *S. aureus, E. coli*, *B. subtilis*, *Proteus vulgaris*, *Vibrio parahaemolyticus* and *Micrococcus luteus*. The results revealed that the methanolic extract showed good inhibition against the tested pathogens (Benrit et al., 2012). Kumara et al. (2017) reported antibacterial activity of *E. antiquorum* latex. The latex showed minimum inhibition only to *E. coli* and *S. aureus*. Latex did not possess antibacterial activity against *Streptococcus agalactiae* and *Pseudomonas aeruginosa*. Sumathi et al. (2011b) tested the methanolic extract of latex for its antibacterial activity against some gram-positive bacteria, *B. subtilis, S. aureus,* and *Shigella flexneri*, and gram-negative bacteria *E. coli* and *Klebsiella pneumoniae* and antifungal activity against *Candida albicans, Aspergillus flavus, A. fumigatus, Rhizopus stolonifer*, and *Mucor indicus*. The results revealed that the latex showed minimum inhibition only to *E. coli* and *S. flexneri*. Latex did possess a strong antifungal activity. Vimal and Das (2015) using disc diffusion method reported antifungal activity against *C. albicans, C. cruzi, C. tropicalis, C. parapolisis*, and *Aspergillus* sps.

50.3.6 WOUND HEALING ACTIVITY

Chowdary et al. (2019) reported wound healing activity of *E. antiquorum.* For the determination of wound healing activity, the wound size for all animals' groups was measured in mm^2. The percentage wound contraction of the control changed from 5^{th} to 20^{th} day is 21.22% to 92.86%. The *E. antiquorum* formulation (2.5%) showed a change from 45.76% to 98.05%

from 5 to 20th day. *E. antiquorum* formulation (5%) showed an increased percentage wound contraction from 72.45% to 99.13% from 5 to 20th day. The 5% ointment showed a significant decrease in wound size when compared with the control group (Chowdary et al., 2019).

50.3.7 INHIBITION OF CANCER CELLS GROWTH

Latex of *E. antiquorum* showed good inhibitory activity on several cancer cell lines. Latex induces apoptosis by morphological change, increased sub-G1 population, DNA fragmentation, and alterations in different levels of apoptosis-associated proteins. Cyclosporine or allopurinol suppressed induced ROS formation. Latex also increased the expression of JNK, FasL, Fas, mitogen-activated protein kinase (MAPK) and reduced the expression of extracellular signal-regulated kinase. Co-treatment with the JNK inhibitor SP600125 activates the caspase -8, -9, and -3 and inhibited *EA*-induced apoptosis. EA causes cell death via apoptotic pathways in HeLa cells (Wen et al., 2012).

50.3.8 MOSQUITOCIDAL ACTIVITY

Vimal and Das (2014) reported mosquitocidal activity of methanolic extract of the latex of *E. antiquorum* against *Ae. aegypti.*

KEYWORDS

- **bioactives**
- **cytotoxicity**
- **Epstein-Barr virus early antigen**
- ***Euphorbia antiquorum***
- **mosquitocidal activity**
- **reactive oxygen species**

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CHAPTER 51

An updated Overview on *Euphorbia hirta* L.

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51.1 INTRODUCTION

Euphorbia hirta L. belongs to the family Euphorbiaceae. The plant is employed to cure several indications; gastrointestinal disorders (diarrhea, dysentery, intestinal parasitosis, bowel complaints, digestive problems), respiratory diseases (cough, cold, asthma, bronchitis, hay fever, emphysema) (Kapoor, 2001), urinary apparatus (diuretic, kidney stone), genital apparatus (metrorrhagic, agalactosis, gonorrhea, and urethritis), various ocular ailments (conjunctivitis corneal ulcer) (Sivarajan and Balachandran, 1994; Colehate and Molyneux, 1993) skin and mucous membranes problems (Guinea worm, scabies, tinea, thrush, and apaththa) and tumor. The latex of the plant is often used for warts and cuts to prevent pathogen infection. The plant is also eaten as a vegetable (Kokwaro, 1993).

These plants are herbs, ascending or prostrate, all parts hirsute with yellow patent spreading multicellular hairs; stems 10–30 cm long, branched; nodes slightly thickened; internodes 2–4 cm long, terete. Leaves asymmetric, oblong-ovate to elliptic-lanceolate, oblique at base, serrate along margins, apex acute, 2–4.5 × 1–1.6 cm, membranous; lateral nerves 3–5 from base; petioles 1–6 mm long; stipules linear-lanceolate, ca 2 mm long, laciniate. Cyathia glomerulate in axillary globose heads, 0.5–1 cm diameter; peduncles dichotomously branched, 2–7 mm long; involucre turbinate ca 1 × 0.5 mm;

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lobes deltoid, acute, ca 1 mm long; glands 4 cupular, 0.5–0.8 mm across; limbs minute or as large as gland, rounded, hyaline, white. *Male florets*: 4–6; pedicels ca 0.8 mm long; anthers sub-globose; bracteoles setaceous, ca 0.5 mm long. *Female floret*: gynophores ca 3 mm long; ovary globose, ca 0.8 mm in diam.; styles ca 0.4 mm long, free, each bifid halfway; stigma capitate. Fruits sub-globose to trigonous, 1.2–2 mm in diam., pubescent; seeds oblong, ca 1 mm long, with 3 or 4 obscure transverse ridges, purplish or reddish gray.

Sandeep et al. (2009); and Huang et al. (2012) reviewed the phytochemistry and pharmacology of *Euphorbia hirta*. Uddin et al. (2019) gave a detailed review on the pharmacology of *E. hirta*.

51.2 BIOACTIVES

E. hirta mainly contains flavonoids, terpenoids, phenols, essential oil, and other compounds. The important constituents of *E. hirta* flavonoids, i.e., quercitrin, quercetin, quercitol, and derivatives containing quercetin-rhamoside, rhamnose, rutin, achlorophenolic acid, leucocyanidin, myricitrin, leucocyanidol, cyanidin 3,5-diglucoside, pelargonium 3,5-diglucoside, and camphol. The flavonol glycoside xanthorhamnin was also isolated from *E. hirta*. The stems contain the myricylalcohol and hydrocarbon hentriacontane. The latex contains inositol, taraxerol, friedelin, β-sitosterol, ellagic acid, kaempferol, quercitol, and quercitrin (Huang et al., 2012).

The aerial parts of *E. hirta* contains terpenoids, including triterpenes: friedelin, α-amyrin, β-amyrin, taraxerol, and its esters: taraxerone, 11,12-oxidotaraxerol, cycloartenol, euphorbol hexacosoate and 24-methylenecycloartenol. The whole plant of *E. hirta* also contain diterpene esters of the ingenol type and phorbol type, ingenol triacetate, 12-deoxyphorbol-13-dodecanoate-20-acetate, 12-deoxyphorbol-13-phenylacetate-20-acetate, as well as the highly toxic tinyatoxin, a resiniferonol derivative. Few new ent-kaurane diterpenoid were isolated from the ethanol extract of *E. hirta* and identified as 16-alpha, 2-beta, 19-trihydroxy-ent-kaurane, 16-alpha-dihydroxy-ent-kaurane, and 16-alpha, 19-dihydroxyent-kaurane (Yan et al., 2011). The sterols, isolated including β-sitosterol, cholesterol, campesterol, and stigmasterol (Hazimi et al., 2008; Baslas and Agarwal, 1980). Tannins isolated from *E. hirta* include the terchebin, dimeric hydrolysable dehydroellagitannins euphorbins A, B, C, E, and the monomeric hydrolysable tannins geraniin, 2,4,6-tri-O-galloyl-D-glucose and 1,2,3,4,6-penta-O-galloyl-D-glucose and the esters 5-Ocaffeoylquinic acid (neochlorogenic acid), and

3,4-di-Ogalloylquinic acid, and benzyl gallate. Acids isolated from *E. hirta* include gallic, ellagic, tannic, tartaric acid, and maleic (Sandeep et al., 2009).

The major components of the essential oil include 3,7,11,15-tetramethyl-2-hexadecen-1-ol, 6,10,14-trimethyl-2-pentadecanone, hexadecanal, phytol, and n-hexadecanoic acid adding up to 61.01%. The minor constituents of *E. hirta* include 2-butoxyethanol, tetradecane, phthalic acid, butyl tetradecyl ester, oleic acid, 13-heptadecyn-1-ol, 2-methyl-1-hexadecanol, and 1,2-benzene dicarboxylic acid diisooctylester (Ogunlesi et al., 2009).

51.3 PHARMACOLOGY

51.3.1 ANTI-INFLAMMATORY ACTIVITY

Shih and Cherng (2010) studied the anti-inflammatory effect of ethanol extract of *E. hirta* and active component – amyrin against lipopolysaccharide (LPS)-activated macrophage cells (RAW 264.7). The extract contains an active component which inhibited iNOS gene expression and nitric oxide (NO) production (Mallavadhani and Narasimhan, 2009). Martinez-Vazquez et al. (1999) isolated and identified triterpens like amyrin, 24-methyl encycliartenol and β-sitosterol from n-hexane extract of *E. hirta*, the n-hexane extract and triterpens were evaluated for anti-inflammatory effects in mice. Ethanol and n-hexane extracts contains triterpenes exerted significant anti-inflammatory effects in TPA-induced ear model. The results revealed that dual and triplet combinations exerted higher activity than triterpene alone (Vázquez et al., 1999). Although *E. hirta* was ineffective in Freund's adjuvant-induced rheumatoid arthritis model, it reduced the inflammatory hyperalgia of rheumatoid arthritis (Lanhers et al., 1991).

51.3.2 ANTI-OXIDATION ACTIVITY

Kumar et al. (2010) carried out antidiabetic and antioxidant effect of *E. hirta* in mice. The ethanol (250 mg/kg) and petroleum ether (500 mg/kg) extracts of flowers *E. hirta* were orally given and tested for 21 days in alloxan-induced diabetic mice. The creatinine, serum cholesterol, triglycerides, alkaline phosphatase (ALP), and urea levels were induced significantly. Total proteins (TPs) and high-density lipoprotein were increased after treatments. The antioxidant assays of all extracts showed antioxidant activity. *E. hirta* flower extract possesses both antidiabetic and antioxidant activity. Basma

et al. (2011) reported the antioxidant activity of *E. hirta*. Methanol extract (ME) of four different parts of plants, leaves, stems, roots, and flowers were tested for *in vitro* antioxidant activity. The IC_{50} values for root, stem, leaves, and flowers and BHT were 0.803, 0.972, 0.989, 1.358, and 0.794 mg/ml. Leaves extract consists of the highest total flavonoid content and total phenolic content, followed by flowers, roots, and stem extracts. Phytochemical screening of *E. hirta* revealed the presence of several chemicals, including flavanoids, which may be responsible for its strong anti-oxidative activity. The antioxidant activity of *E. hirta* was comparable with that of ascorbic acid and was found to be dose-dependent (Basma et al., 2011).

51.3.3 ANTI-TUMOR ACTIVITY

Chi et al. (2012) isolated a new cylcopentanone derivative (1′R,5′R)-5-(5′-carboxylmethyl-2-oxocyclopentyl)-3Z-pentenyl acetate from *E. hirta*. The cytotoxicity of ethanol extract of *E. hirta* was evaluated against K562 (human leukemia) and A549 (lung cancer) cell lines. From the data, the ethanol extract exhibited a weak activity against A549 cells (inhibition ratio 15.02 ± 11.60%) and inactive against K562 cells.

51.3.4 ANTI-DIABETIC AND FREE RADICAL SCAVENGING ACTIVITY

Uppal et al. (2012) evaluated the antidiabetic activity of the ethanol extract of *E. hirta* using animal screening models. Alloxan was administered for 21 days, to induce diabetics. The ethanol extract showed a significantly decreased blood glucose level on alloxan-induced diabetic rats. *In vitro* and *in vivo* study of antidiabetic activity was tested by Widharna et al. (2010), from the *in vitro* experiment, reported that ethanol extract and ethyl acetate (EAE) fractions had glucosidase inhibition activity, while n-hexane, chloroform, butanol, and water fractions had no glucosidase inhibitory effect, *in vivo* test, also revealed same results. Based on *in vitro* and *in vivo* tests, *E. hirta* EAE extract and ethanolic extract (EE) exerted antidiabetic mechanism and glucosidase inhibitory properties.

51.3.5 ANTIARTHRITIC ACTIVITY

Ahmad et al. (2012) investigated the antiarthritic activity of *E. hirta* in animal models. Adjuvant arthritis induced by sub-plantar injection of 0.05 ml freshly

prepared suspension (5.0 mg/ml) of steam-killed *Mycobacterium tuberculosis* (MTB) in liquid paraffin. Different doses of 200, 100, 50, and 25 mg/kg of ethanol extract were used for treatment. *E. hirta* significantly reduced IL-1. TNF-, IL-2 and IFN-in splenocytes of arthritic rats and downregulated LPS-induced nitric oxide (NO) production in peritoneal macrophages. This result suggests that *E. hirta* showed an improved adjuvant-induced arthritis.

51.3.6 ANTIALLERGIC ACTIVITY

Singh et al. (2006) described an antiallergic reactions of 95% EE prepared from whole aerial parts of *E. hirta* (EH A001). EH A001 significantly inhibited rat peritoneal mast cell degranulation triggered by compound 48/80, dextran-induced rat paw edema. It prevented eosinophil peroxidase activity and eosinophil accumulation and reduced the protein content in bronchoalveolar lavage fluid (BALF). Extract suppressed the CD8/CD4 ratio in peripheral blood. It also attenuated interleukin-4 (IL-4) release and augmented interleukin-(IFN-) in ovalbumin-sensitized mouse splenocytes. The results compared with cetirizine and ketotifen, cyclophosphamide, known compounds, and proved that *E. hirta* showed significant activity to prevent early and late phase allergic reactions.

51.3.7 ANXIOLYTIC AND SEDATIVE PROPERTIES

Anuradha et al. (2008) studied the anxiolytic effect of hydroalcoholic extract of *E. hirta* (Eh), forced swim stress (FSS), and Chronic immobilization (CIS) was induced in rats. Eh (200 mg/kg p.o), marked anti-anxiety activity in CIS and partially decreased activity in FSS observed for seven days. Contra treatment of rats with flumazenil (0.5 mg/kg i.p), bicuculline (1 mg/kg i.p) resulted in a significant reduction in the anxiolytic effect of Eh. This indicates that anxiolytic activity is mediated through GABAA receptor, benzodiazepine receptor Channel complex. The results revealed that Eh acts as a potential anxiolytic drug. Lanhers et al. (1990) found behavioral effects of *E. hirta,* in mice. Lyophilized aqueous extract of *E. hirta* not showed any mortality when administered i.p. and orally. Decrease and increased behavioral parameters were measured by activities and staircase test at a high (100 mg of dried whole plant/kg) and lowest dose (25 mg and 12.5 of dried whole plant/kg). These findings support the traditional use of *E. hirta* an anxiolytic and sedative property.

51.3.8 ANTI-DIARRHEAL AND SPASMOGENIC ACTIVITY

Kamgang et al. (2001) investigated the contractile activity of total aqueous extract of *E. hirta* leaves in rat. Aqueous extract of *E. hirta* activated the stimulation of rat ileal contractions by potassium chloride (+381%) and acetylcholine (+148%). *E. hirta* aqueous extract also reduced the fecal quantity (12 g). The result confirmed that the total aqueous extract of *E. hirta* had an antidiarrhoeic effect *in vivo* and a spasmogenic effect *in vitro*.

51.3.9 ANALGESIC AND ANTI-ANAPHYLACTIC ACTIVITY

E. hirta ethanol extract (EH A001) administered orally (100 to 1,000 mg/kg) against compound 48/80 induced systemic anaphylaxis. The data showed that EH A001 inhibited passive cutaneous anaphylaxis (PCA) in rats and active paw anaphylaxis in mice. The result also showed a suppressive effect on TNF- and IL-6 release from anti-DNP-HAS-activated rat peritoneal mast cells (Youssouf et al., 2007).

51.3.10 DIURETIC EFFECT

Johnson et al. (1999) studied the diuretic activity of *E. hirta* leaf extracts in rats using acetazolamide and furosemide, standard diuretic drugs. A time depended on an increase in urine output was observed with ethanol and aqueous extracts (100 and 50 mg/kg). From the result, it was found that aqueous extract increased the urine excretion of K^+, HCO^{3-} and Na^+, and urine output like acetazolamide. Ethanol extract increased the excretion of HCO^{3-} loss. The active component in the aqueous extract of *E. hirta* had a similar diuretic effect as acetazolamide, a standard drug. These results support the traditional use of *E. hirta* as a diuretic agent.

51.3.11 EFFECT ON GASTROINTESTINAL TRACT

Gastrointestinal motility in rats and mice has been studied by Hore et al. (2006). The results revealed that aqueous leaf extract significantly and dose-dependently decreased castor oil-induced diarrhea in mice and gastrointestinal motility in rats. These findings supported the traditional use of *E. hirta* in diarrhea.

51.3.12 SPERM MOTILITY

Oyeyemi et al. (2009) utilized sexually matured and healthy West African Dwarf (WAD) rams. The rams aged between 24 and 30 months were used for the study. Experimental animals were orally dosed with 400 mg/kg body weight for 14 days. Semen samples were collected after a day and seven days after administration. Semen picture showed a significant reduction of sperm motility from 80% to 47.5% and live dead ratio from 90.75% to 32.5%. This result indicated that fertilization capacity and livability of spermatozoa were negatively affected. But no significant difference in values of body parameters was found. Thus *E. hirta* was not recommended for medicinal purpose in male animals.

51.3.13 EFFECT ON CNS

Lanhers et al. (1996) evaluated lyophilized aqueous extract of *E. hirta* (Eh) for benzodiazepine-like properties, hypnotic, neuroleptic, and antidepressant properties. The result revealed that aqueous extract does not possess to benzodiazepine-like properties hypnotic or neuroleptic effect. *E. hirta* plant extract caused slight depressant effect and a direct action on the central nervous system (CNS).

51.3.14 EFFECT ON ASTHMA

Pretorius et al. (2007) made a comparative ultra-structural analysis of fibrin networks and platelets using murine Balb/c asthma model. Ultra-structure of platelets and fibrin networks of control compared with asthmatic mice, treated with one concentration of plant material and two concentrations of hydrocortisone. Control mice possess minor thin fibers and major thick fibers and tight round platelet aggregates with pseudopodia formation. Asthmatic mice have major fibers covered with net-like minor fibers and loosely connected granular aggregates of platelets. Hydrocortisone of both concentrations made the fibrin more fragile and more granular platelet aggregate, whereas *E. hirta* have prevented the minor fibers to form a dense net-like layer over the major fibers and no impact on the fragility of fibrin.

51.3.15 TOXICITY

Patil and Ngdum (2011) determined LC_{50} using shrimp lethality assay. Extracts of *E. hirta* and *E. nerifolia* were chosen for brine shrimp lethality activity. LC_{50} of EAE, acetone extract of *E. hirta* and ME of *E. nerifolia* were found to be 71.15, 92.15, and 49.55 g/mL, respectively. Among these two plants, the most active extract was ME of *E. nerifolia*. Yadav and Singh (2011) studied the efficacy of tertiary and binary combinations of *E. hirta* latex powder with other active compounds like rutin, ellagic acids, teraxerol, and betulin. Toxic effect of *E. hirta* active compounds and latex were evaluated against *Indoplanorbis exustus* and freshwater snails *Lymnaea (Radux) acuminata* in pond. The freshwater fish *Channa punctatus* (Bloch) and with snails, were also lethal to high dose, while LC_{90} not showed the significant killing properties in fish populations.

51.3.16 ANTI-BACTERIAL/ANTI-FUNGAL ACTIVITY

Alisi and Abanobi (2012) isolated gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli, Salmonella typhi*, from degenerated wound, stool, and a high vaginal swab. Total dehydrogenase activity was assayed using 2,3,5-triphenyl tetrazolium chloride (TTC). Inhibitory activity of EE of *Euphorbia hyssopifolia* and *E. hirta* was compared with standard antibiotics ciprofloxacin and gentamicin. A dose-depended inhibition was observed. *E. hyssopifolia* was effective against gram-positive *Staphylococcus aureus*, then gram-negative *S. typhi* and *E. coli*. *E. hirta* was effective against gram-negative *S. typhi* and *E. coli*, but not effective against *S. aureus*. Hence, *E. hirta* can be implicated against urinary tract infections and typhoid fever. Titilope et al. (2012) reported the antibacterial activity of dry and fresh leaf extracts (water and ethanol) against some pathogens, *Haemophilus influenzae, E. coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, S. aureus, S. typhi,* and *Shigella dysenteriae.* Antibacterial sensitivity test indicated that *E. hirta* extracts had less or no zone of inhibition against *H. influenzae*. Hence, dry extract produced the highest zone of inhibition on all pathogens than fresh extracts.

51.3.17 BURN WOUND HEALING PROPERTIES

Tissue damage from electricity, excessive heat, corrosive chemicals or radioactivity that destroy protein in the exposed cells is called a burn. They permit loss of body fluid, microbial invasion and infection loss of thermoregulation.

E. hirta plant extracts exhibited antimicrobial activity against various microbes, including those causing burn and wound infections like *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Sudhakar et al., 2006; Rajeh et al., 2010). Hence, *E. hirta* could be beneficial to reduce the effect of burn wounds. The ethanol extract of the whole plant of *E. hirta* was used for burning wound healing activity in rats as 2% W/W cream. The experiments carried out were based on the assessment of the percentage reduction in original wounds. *E. hirta* showed significant burn wound healing activity (Jaiprakash et al., 2006).

51.3.18 MOLLUSCICIDAL AND LARVICIDAL ACTIVITY

Larvicidal activity of *E. hirta* has been found in petroleum ether extract with LC_{50} value of 272.36 ppm (Rahuman et al., 2008). The two diseases, schistosomiasis and fascioliasis, carried by aquatic snails, cause immense harm to domestic animals and humans. The freshwater vector snail *Lymnaea acuminata* is the intermediate host of *Fasciola gigantica* and *F. hepatica*. These are causes for endemic fascioliasis in sheep, cattle, goats, and other herbivorous animals. Aqueous leaf and stem bark extracts of plant *E. hirta* showed significant molluscicidal activity. Sub-lethal doses (80% and 40% of LC_{50}) of aqueous leaf and stem bark extract and also showed alter the levels of total free amino acid, TP nucleic acids (DNA and RNA) and the activity of ALP, enzyme protease and in various tissues of the vector snail *L. acuminata* in time and dose-dependent manners (Singh et al., 2005).

KEYWORDS

- **bioactives**
- **chronic immobilization**
- ***Euphorbia hirta***
- **larvicidal**
- **lipopolysaccharide**
- **pharmacology**

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CHAPTER 52

Phytochemical and Pharmacological Profile of *Euphorbia neriifolia* L. (Indian Spurge Tree)

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52.1 INTRODUCTION

Euphorbia neriifolia L. (Syn.: *Euphorbia ligularia* Roxb.), Euphorbiaceae, known as milk hedge, is a succulent small tree, originated from South Asia, and usually grows around dry, rocky, and hilly areas of south Asian countries. The significant secondary metabolites present in *E. neriifolia* are alkaloids, flavonoids, saponins, glycosides, phenolic steroids compounds, etc. The different plant parts like roots, stem, bark, leaf, flower, fruit, and whole plant are used for varied aliments as well as in medicine from ancient times. The usages were recommended in "Charaksamhita," an ayurvedic classic and other traditional medicinal systems.

Euphorbia neriifolia plants are shrubs or small trees, erect, 2–6 m tall, fleshy, and slightly succulent, branches crowded, curved upwards, with 5 spiral ridges, obtusely 5-angled, pale gray green; podaria in 5 vertical spiral rows, spines 2, divaricate, 4–5 mm long, black, sharp. Leaves alternate, sessile or subsessile, crowded at ends of branches, obovate-oblong, narrowly oblanceolate to spathulate, tapering to cuneate at base, entire, obtuse to acute at apex, fleshy, smooth, dark green on upper surface, pale green on lower surface, glabrous, shiny, deciduous when in flower; cyathia solitary, in diads or triads above podarium, the central cyathium sessile and staminate,

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the lateral ones pedunculate and with both staminate and pistillate florets; involucres cupular, bracts 2, ovate, involucral lobes 5, suborbicular, wavy or toothed along margin, ca 3 mm long, yellow; glands 5. Staminate florets in 4–5 fascicles of 3 or 4 flowers in each. Pistillate florets; gynophores ca 3 mm long ovary obscurely 4- or 5-angled; styles connate to middle; stigma papillose. Fruits 5–8 mm in diam., 3-angled, smooth, glabrous, seeds globose, ca 3 mm diam, smooth, caruncle small white.

Common names include: Sanskrit: Snoohi, vajra, vijri, patrasnuk, svarasna, upavisha; Hindi: Sehund, Sij, Patton-ki-send, Thohar; Bengali: Mansasji, Hij-daom, Patasij, Telugu: Akujemudu, English: Common milk hedge Arabic: Dihu Minguta; Kannada: Elekalli, Murukaninakalli; Gujarathi: Bhungarathor; Tamil: Ilai-k-kalli; Malayalam: Kalli, Kaikalli; Punjabi: Thor; Marathi: Tridharanivdunga.

52.2 BIOACTIVES

Phytochemical investigations on *Euphorbia neriifolia* yielded secondary metabolites of different classes such as euphol (8,24-euphadien-3β-ol), monohydroxy triterpenes, nerifoliol, taraxerol, flavonoids, steroidal saponins, sugar, tannins, alkaloids, β-amyrion, glut-5(10)-en-1-one, cycloartenol, 9,9-cylolanost-20(21)ene-24-ol-3-one (neriifolione), and triterpenoidal saponin (Ilyas et al., 1998; Anjaneyulu and Row, 1965). Chemical constituent present in different part of plant are euphol (whole plant, bark, latex, root); friedelan-3 and 3β-ol, D:B-friedoolen-5(10)-en-1-one, glut-5(10)-en-1-one and taraxerol (stem, leaves); n-hexacosanol, euphorbol, hexacosanoate, 12-deoxy-4β-hydroxyphorbol-13-dode-canoate-20-acetate and pelargonidin-3,5-diglucoside (bark); 24-methylenecycloartenol and tulipanindiglucoside (bark, root); nerifoliol (latex), cycloartenol, euphorbol, ingenol triacetate, 12-deoxyphorbol-13,20-diacetate, delphinidin-3,5-diglucoside (root) (Anjaneyulu and Row, 1965; Chatterjee et al., 1978).

52.3 PHARMACOLOGICAL ACTIVITIES

52.3.1 ANESTHETIC ACTIVITY

The aqueous and alcoholic extract of *E. neriifolia* stem evaluated for anesthetic activity by using foot-withdrawal reflex method in frog and intradermal wheal method in guinea pig. *E. neriifolia* alcoholic stem extract

possesses good anesthetic action. However, aqueous extract does not reflect such action (Lahon et al., 1979).

52.3.2 ANALGESIC ACTIVITY

Hydroalcoholic extract of leaves of *E. neriifolia* has been evaluated for analgesic activity by using Eddy's hot plate and tail flick method. The extract showed potential analgesic activity, which is comparable to diclofenac sodium (Gaur et al., 2009b). Hydroalcoholic extract of leaves (400 mg/kg) using mechanical, thermal, and chemical stimulus revealed that the extract significantly inhibits pain (432.22%) threshold after 60 min. The hydroalcoholic extract treatment increases tail flick and tail clip at 45 min. The acetic acid-induced writhing episode protection is 53.83% at the above dose (Bigoniya and Rana, 2010).

52.3.3 ANTI-ANXIETY, ANTI-CONVULSANT, AND ANTI-PSYCHOTIC ACTIVITY

The hydroalcoholic leaf extract of *E. neriifolia* used for anti-anxiety anti-convulsant and anti-psychotic have been reported by Bigoniya and Rana (2005). The hydroalcoholic extract reduces apomorphine-induced stereotypy. It shows significant effect on specific dopaminergic receptor modulating action. It also showed the protective effect against maximal electro-shock-induced convulsion and anxiolytic action in elevated plus-maze.

52.3.4 ANTI-ARTHRITIS ACTIVITY

The chemical compound neriifolione has been isolated from latex of *E. neriifolia*, used for against anti-arthritis activity, by using Fruend's adjuvant arthritis model in rats. The administration of oral neriifolione (0.2 mg/100 gm) showed 51% inhibition of paw volume. However, it was found to be more toxic. Therefore, it appears to be less promising clinically (Ilyas et al., 1998).

52.3.5 ANTI-DIARRHEAL ACTIVITY

Hydroalcoholic leaf extract *E. neriifolia* is reported by Bigoniya and Rana (2010), to have anti-diarrheal activity in rats using castor oil-induced diarrhea model. The extract showed a laxative effect by increase in soaked defecation along with castor oil (Bigoniya and Rana, 2010).

52.3.6 ANTI-INFLAMMATORY/ANTI-THROMBOTIC EFFECT

The anti-inflammatory activity of petroleum ether fraction of latex by Bigoniya et al. (2010), in carrageenan induced rat paw edema. The petroleum ether fraction of latex inhibits 42.40 and 35.25% edema at the dose levels of 750 and 500 mg/mL which are present in latex, triterpenes like, euphol, cycloartenol, and nerifoliol (Bigoniya et al., 2010). Hydroalcoholic extract of leaves reduces mean paw volume in carrageenan treated rats and in cotton pellet induced granuloma extract showed considerable anti-inflammatory property (Gaur et al., 2009b; Bigoniya and Rana, 2010). Petrol-benzene and acetone extracts from dried latex and isolated cycloartenol and neriifolione from the latex of *E. neriifolia* were evaluated (Ilyas et al., 2003). Petroleum ether and ethanol extract of roots and leaves of *E. neriifolia* showed significant anti-thrombotic activity (Hasan et al., 2010).

52.3.7 ANTICARCINOGENIC/RENAL CARCINOGENESIS/ HEPATOCARCINOGENESIS ACTIVITY

Saponins reported in the leaf of *E. neriifolia* have been studied against CCl_4-induced hepatotoxicity. The treatment increases serum glutamic pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), and alkaline phosphatase (ALP) levels and notably improves histopathological alterations. The sleeping time induced by thiopentose, has been decreased by the saponin fraction. The saponins also restored the reduced glutathione (GSH) and depleted hepatic superoxide dismutase (SOD), leaves by enhancing the antioxidant status at liver. The hydro-ethanolic extract of *E. neriifolia* showed a protective effect on diethyl nitrosamine (DENA) induced abnormalities in non-enzymatic, metabolic enzymatic and biochemical parameters has been reported by Sharma et al. (2011).

DENA treatment significantly decreased the glutathione-S-transferase (GST) and GSH content and increased SGPT, SGOT, and ALP level. *E. neriifolia* leaf extract also showed its chemo-preventive property by improving the levels of antioxidant and alleviating raised biochemical parameters in DENA generated carcinogenesis by reducing the formation of free radicals and exhibiting anticarcinogenic properties. The flavonoid which was isolated from leaves was investigated against DENA induced renal carcinogenesis. The renal marker like serum urea and creatinine, xenobiotic markers like Cyt b5 and Cyt P450 catalase (CAT), lipid peroxidation (LPO), SOD, GSH,

and GST along with levels of SGOT, ALP, SGPT, total cholesterol (TC) and total protein (TP) were considered to find out progression of the renal carcinogenesis. DENA treatment has enhanced the Cyt P450, Cyt b5 and LPO levels and decreased SOD, GST, CAT, and GSH levels. Flavonoid fraction isolated from *E. neriifolia* used for neutralized the oxidative stress induced by DENA and exert its defensive property by regaining the normal levels of, GST, SOD, GSH, CAT, SGPT, SGOT, TC, ALP, urea, TP creatinine, Cyt P450 and Cyt b5. Animals that were treated with DENA showed the alterations in normal renal histo-architecture with characteristic inflammation and necrosis (Sharma et al., 2011, 2013; Pracheta et al., 2011a). Effect of DENA on the liver has been studied and it was found that hydroethanolic extract and isolated flavonoid fraction showed hepatic protective effect (Sharma and Janmeda, 2014; Pracheta et al., 2011c).

52.3.8 ANTIMICROBIAL ACTIVITY

Various extracts used for antimicrobial activity viz., ethanol, chloroform, butanol, ethyl acetate (EAE), and aqueous of leaves of *E. neriifolia* was studied using *Staphylococcus aureus, Klebsiella pneumoniae*, *E. coli*, *Pseudomonas vulgaris* and *Pseudomonas fluorescens*. The good inhibition was seen with chloroform extract (CE) in *P. vulgaris* with the zone of inhibition of 8 mm followed by ethanol extract against *Klebsiella pneumoniae* with the zone of inhibition of 5 mm. The water and EAE extract exhibit very less effect (Kumara et al., 2011). Antimicrobial activity of ME of *E. neriifolia* stem was assessed against *E. coli* (K-88), *Salmonella typhi* (12), *Staphylococcus aureus* (ATC-2245), *Pseudomonas aeruginosa, P. vulgaris* (CC-52), *Aspergillus niger* (36) and *Candida albicans* using disc diffusion and microdilution assays (Datta et al., 2013). The results of these assays have ensured that the stem of *E. neriifolia* possesses significant antimicrobial activity which was comparable to that of standard drugs.

52.3.9 ANTIDIABETIC ACTIVITY

Ethanolic extract (EE) of leaves of *E. neriifolia* against alloxan-induced diabetic model in rats was reported by Mushir and Patel (2012). Different parameters such as fasting blood glucose level, oral glucose tolerance test and serum lipid levels were assessed. Among these oral glucose tolerance test showed a decrease in fasting blood after 60 min of drug administration.

The animals showed maximum reduction of fasting blood glucose after 15 d, at the dose 400 mg/kg. Reduced serum lipids were observed, which was comparable to the normal group rats.

52.3.10 ANTIULCER ACTIVITY

E. neriifolia leaves hydroalcoholic extract showed potential antiulcer activity, at 400/mg/kg was tested against pyloric ligation and ethanol induced gastric ulceration models. The increased levels of extract were observed for total hexosamine, total carbohydrates, total hexoses and sialic acid content with reducing levels of protein content of gastric juice. Treatment with extract reduced ulcer index (Bigoniya and Rana, 2010).

52.3.11 ANTIOXIDANT ACTIVITY

E. neriifolia leaves showed good antioxidant activity. The effect of saponins present in leaves was evaluated by using various methods reducing power, hydrogen donating ability, anti-LPO, and scavenging activity by superoxide and hydroxyl radicals. Saponins showed potent antioxidant activity for all five assays except scavenging activity by hydroxyl radicals (Bigoniya and Rana, 2017). The hydroalcoholic extract of leaves used for antioxidant activity, using inhibition of DPPH, H_2O_2, superoxide anions, reducing power metal chelating capacity and FRAP activity was evaluated by Kumara et al. (2011). Percent inhibition of LPO showed antioxidant activity of 76.15% compared to that of ascorbic acid (75.6%), butylated hydroxyanisole (BHA) (60.8%) and butylated hydroxytoluene (BHT) (75.6%). The capacity of metal chelating was to be 73.24%. Euphanol isolated from *E. neriifolia* leaves was carried out for antioxidant activities using hydroxyl radical, DPPH, reducing power and superoxide radical scavenging assays. The chemical constituent euphol exerts free radical scavenging activity and hydrogen donating capacity which is comparable to a-tocopherol (Bigonia and Rana, 2009). The leaf extract was also evaluated by FRAP, TAC, FTC, TBA, and non-specific activity assays. The extract possessed antioxidant properties (Pracheta et al., 2011b). Potentiality of leaf extract on rat kidneys and liver was tested by using various histological, hematological, biochemical, and antioxidant enzyme parameters for the period of 21 and 45 days. The extract showed a considerable increase in liver and kidney SOD and CAT with a decrease in LPO (Bigoniya and Rana, 2017).

52.3.12 CYTOTOXICITY ACTIVITY

Euphol isolated from triterpenoidal sapogenin fraction of *E. neriifolia* leaves was used for *in vitro* cytotoxicity assay using murine F1B16 melanoma cell line. The assay revealed that 173.78 mg/ml concentration shows 50% inhibition (Bigoniya and Rana, 2009a). Methanolic extract of *E. hirta*, *E. neriifolia*, *and E. tirucalli* tested for against B16F10 melanoma cancer cell line. All plants showed significant cytotoxicity on B16F10 melanoma cell line in concentration range of 10–1,000 mL using MTT and SRB assay. The inhibition of 50% of methanolic extract of *E. hirta*, *E. tirucalii*, and *E. neriifolia* was 185.41, 20.10, and 198.26 by SRB assay and 240.98, 237.07, and 212.78 by MTT assay. The extracts revealed significant activity against B16F10 melanoma cells (Babar et al., 2012). LC_{50} rate of methanol, EAE and acetone extracts of *E. hirta* and *E. neriifolia* was also determined by using brine shrimp lethality assay. LC_{50} value of methanolic extract of *E. neriifolia*, acetone, and EAE extracts of *E. hirta* was found 49.55, 92.15, and 71.15, mg/mL, respectively (Patil and Magdum, 2011).

52.3.13 DERMAL IRRITATION AND SENSITIZATION

The acetone, petroleum ether, chloroform, and water fractions of *E. neriifolia* dried latex were prepared for dermal irritation tests in rabbits. Non-irritating with primary irritation index (PII) score of 0.43/0.11 for erythema observed in petroleum ether fraction. Chloroform, acetone, and water fractions reported skin irritation because of the presence of high diterpene content (Bigoniya et al., 2010).

52.3.14 HEMOLYTIC ACTIVITY

Saponins isolated from *E. neriifolia* leaf was carried out using hemolytic index assay. The 300 mg/mL concentration of crude saponins was showed significant lytic effect against erythrocytes. Moreover, 100 mg/mL concentration of triton showed 100% hemolysis and 100 mg/mL concentration was showed 97.05% hemolysis (Bigoniya et al., 2017).

52.3.15 IMMUNOMODULATORY ACTIVITY

The alcoholic extract of leaves of *E. neriifolia* by non-specific and specific immune response assays was assessed by Bigoniya and Rana (2008). Extract revealed good phagocytic potential in lymphocyte count. Extract

significantly potentiated delayed-type hypersensitivity reaction in rats against sheep red blood cells (SRBC) at 48 h (12.24%) and 24 h (20.63%) and after treatment. Leaf extract (400 mg/kg) has stimulated the humoral immune response that exhibited 270.88% increment in antibody titer after 21 d treatment. *E. neriifolia* is a potential immunostimulant which stimulates cell mediated immunity as well as stimulates phagocytosis. Extract showed significant increased hemopoietic activity and increased survival rate of rats. Immunomodulatory activity of hydroalcoholic extract of *E. neriifolia* dried leaves were assessed using carbon clearance, survival rate, footpad swelling and hemagglutination antibody titer assays (Gaur et al., 2009a).

52.3.16 DEATH-RECEPTOR EXPRESSION ENHANCING ACTIVITY

The seven cycloartane triterpenes, euphonerins A–G (1–7), 3-O-acetyl-8-Otigloylingol (8) and ingol diterpenes isolated from the *E. neriifolia* leaves ME along with 3,12-di-O-acetyl-8-Otigloylingol (9), 03 known flavonols (11–13), (24R)-cycloartane-3b,24,25-triol (10) were studied. Among these compounds, 1–11 showed death-receptor 5 expression enhancing property (Toume et al., 2011).

52.3.17 RADIOPROTECTIVE PROPERTY

The radioprotective property of euphol isolated from the leaves of *E. neriifolia* was assessed against radiation-induced chromosomal aberrations by Bigoniya and Rana (2009a). Pre-treatment with 75 mg/mL of euphol reduced 33.5% of total chromosomal aberrations as compared to 71.5% after radiation treatment alone at 4 Gy.

52.3.18 ANTI-SCORPION VENOM ACTIVITY

Anti-scorpion venom activity was tested for 64 plant species. The *Heterometrus laoticus* scorpion venom treatment against fibroblast cell lysis *E. neriifolia* showed more than 40% effectiveness against cells treated with venom (Nunthawun et al., 2006).

52.3.19 WOUND HEALING PROPERTY

The aqueous extract of latex of *E. neriifolia* was evaluated using guinea pigs (Rasik et al., 1996). The healing process by increasing the tensile strength

due to extract, epithelization, DNA content, and angiogenesis was significant. Excision wound and dead space wound methods were also evaluated. Extract showed considerable improved hydroxyproline content, protein content, and CAT level and decreases in SOD level in granulation tissue (Bigoniya and Rana, 2007).

KEYWORDS

- **anticarcinogenic**
- ***Euphorbia neriifolia***
- **immunomodulator activity**
- **serum glutamic pyruvic transaminase**
- **serum glutamic-oxaloacetic transaminase**
- **wound healing activity**

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CHAPTER 53

Phytochemical and Pharmacological Profile of *Euphorbia thymifolia* L.

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53.1 INTRODUCTION

Euphorbia thymifolia L. (family Euphorbiaceae) is used as sedative, blood purifier, stimulant, laxative, demulcent, anthelminthic, and astringent in diarrhea and dysentery and constipation (Khare, 2004; Prasad and Bisht, 2011; Sikdar and Dutta, 2008). The oil is used in the treatment of erysipelas and medicinal soap preparation. Plant juice and powder are used to cure the ringworms. The seeds, leaves, and whole plant are used as stimulants, worm infections, and astringent (Kirtikar and Basu, 2006; Gupta et al., 2007; Khare and Berline, 2004; Sikdar and Dutta, 2008).

Euphorbia thymifolia plants are herbaceous, grow up to 30 cm, puberulous; stems spreading, radiating from woody rootstock, branched; nodes thickened; internodes 1–2 cm long, terete. Leaves distichous, ovate-oblong, oblique at base, crenulate-serrulate or entire up to middle, obtuse or sub-acute at apex, 3–8×2–5 mm, glabrous above, scattered hairy beneath, 3-veined at base; petioles 0.5–1 mm long. Cyathia terminal or on short axillary microphyllous shoots, solitary or few together, subtended by several minute leaves; involucres turbinate; lobes 5, small, triangular, ciliate; glands 4, suborbicular, purplish red; limbs white-pink. *Male florets*: anthers sub-globose; bracteoles filiform. *Female floret*: gynophores ca 5 mm long; ovary subglobose, pubescent; styles free, each bifid, stigma capitate. Fruits sparsely

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exerted from involucral cup, trigonous-sub-globose, obtusely keeled, hispid; seeds oblong, tetragonal, bluntly pointed, transversely 2 or 3-furrowed, reddish brown.

53.2 BIOACTIVES

Prasad and Bisht (2011) reported, tetradeconoic acid, cymol, 2-(4-methyl-3-cyclohexene-1-yl)-2-proanol, isopinocamphenol, limonene, 2,4-decadienal, A-caryophyllene, 2,6,6-trimethyl-1-cyclohexane-1-carboxaldehyde, safranal, 2,4-heptadienal, piperitone, 1-pentanol, benzaldehyde, 2,3-heptadione, phytol, pentadecanoic acid, caryophyllene oxide, n-hexadecanoic acid, 2-n-pentylfuran, nonanal, macro-minerals (Ca, Na, K, Li), micro-minerals (Cu, Co, Fe, Mn), -carotene, Chlorophyll a and b, vitamin-C, tannins, phenolics, crude fat, crude protein, starch, crude fiber, total carbohydrate, amylase, cellulose, amylopectin. Rastogi and Mehrotra (1993) reported cosmosiin, kaempferol, salisylic acid, carvacrol, 2-sesquiterpenes, pedunculagin, sterol, n-alkanes, esters, cholesterol, β-amyrine, 12-deoxy-4-b-hydroxyphorbol-13-phenyacetate-29-acetate, 1 and 5-desgalloylstachyruin, epitaraxerol, corilagin, β-sitosterol, phorbal derivatives, geraniin, eugeniin, quercetin-3-rhamnoside, stigmasterol, bixanin, 12-deoxy-4-hydroxyphorbol-13-dodecanoate-20-acetate, 12-deoxyphorbol-13, 20-diacetate, casuariin, n-hexacosanol, euphorbol, and two derivatives of deoxyphorbol-OAC.

53.3 PHARMACOLOGICAL ACTIVITIES

53.3.1 ANTIHYPERGLYCEMIC ACTIVITY

Euphorbia thymifolia extract was used to analyze the oral glucose tolerance test. Around 2 h after glucose administration, serum glucose levels were measured. The extract showed significant dose-dependent reduction in serum glucose levels in mice. When administrated at doses 400, 200, 100, 50 mg/kg body weight. Maximum reduction of serum glucose was observed in 400 mg/kg, compared with standard glibenclamide. When administered at a low dose of 10 mg/kg body weight, it decreases serum glucose levels by 48.6% (Rahmatullah et al., 2012).

53.3.2 ANTINOCICEPTIVE ACTIVITY

Mice were used to evaluate antinociceptive activity by using acetic acid-induced writhing. The extract showed significant dose-dependent

antinociceptive activity. The number of abdominal writhing was inhibited by 49.0% obtained with a standard antinociceptive drug aspirin, administered at a dose of 200 mg/kg body weight, compared to dose of 400 mg/kg body weight, the number of abdominal writhing was inhibited by 40.9% (Rahmatullah et al., 2012).

53.3.3 ANTI-HSV-2 ACTIVITY

Ethyl acetate (EAE) extract and 3-O-galloyl-4,6-(S)-hexahydroxydiphenoyl-d-glucose used to study *In-vitro* anti-HSV-2 activity. The result revealed that ethyl extract and 3OG46HG affected virus infectivity in a dose-dependent manner. The extract of EAE reduced virus infectivity at a concentration of 4.0/ml. Whereas, 3OG46HG obviously diminished virus infectivity at a concentration of a 0.5/ml. The virucidal ability of the EAE extract of *E. thymifolia* was not affected by the incubation temperature but it effected the incubation period. In the case of the action of 3OG46HG against HSV-2, the effects of temperature and incubation time were negligible (Yang et al., 2005). By using fractions of 3-O-galloyl-4,6-(S)-HHDP-D-glucose and EAE antiviral activity or Anti-HSV-2 was also evaluated (Lin et al., 2002).

53.3.4 ANTIOXIDANT OR FREE RADICAL SCAVENGING/ANTI-SUPEROXIDE/ANTI-LIPID

E. thymifolia whole plant ethanol extract has been evaluated for *in-vitro* and *in-vivo* antioxidant activity experimental models for estimating the malondialdehyde (MDA) content of rat brain. It is one of the products of the LPO.

E. thymifolia ethanolic extract (EE) showed potential inhibition of LPO and vitamin E used as a standard (Prabha and Singh, 2005). Antioxidant or free radical scavenging, anti-superoxide formation, and anti-lipid activities of *E. thymifolia* plant extract were investigated using different fractions, i.e., $CHCl_3$, MeOH, n-butanol, EtOAc, water, and compounds rugosin B, (3-O-galloyl-4,6-(S)-HHDP-D-glucose and 1,3,4,6-tetra-O-galloyl-K-beta-D-glucose), with the exception of the organic aqueous fraction in the anti-superoxide and anti-lipid and formation assays. The IC_{50} values of anti-superoxide formation, anti-lipid formation, and free radical scavenging assays for pure compounds and all fractions a were 0.03–2.18, 2.81–7.63, and 0.013–2.878 mg/ml, respectively. The Electron spin resonance studies showed that pure compounds and water extracts (WEs) of *E. thymifolia*

exhibited hydroxyl radical scavenging and superoxide radical activities (Lin et al., 2002). Antioxidant activity of *E. thymifolia* whole plant ethanolic was extract evaluated using extract of the whole plant. The Griess's method used for to evaluate antioxidant activity. The extract inhibited nitric oxide (NO) free radical, and it was estimated by that the use of Griess reagent. The results revealed that *E. thymifolia* extract showed a significant antioxidant effect (Nagaraju et al., 2012).

53.3.5 ANTI-INFLAMMATORY ACTIVITY

The whole plant ethanol extract of *E. thymifolia* was evaluated anti-inflammatory activity. The EE in the dose of 100 mg/kg body weight showed a comparable reduction with that of the standard drug, Indomethacin (10 mg/kg). The results revealed that the extract possesses significant anti-inflammatory activity (Nagaraju et al., 2012).

53.3.6 ANTISPASMODIC ACTION

E. thymifolia EE was used for to analyze antispasmodic activity. The results showed that the EE was able to inhibit the growth of *Plasmodium falciparum* (Mon et al., 2008).

53.3.7 ANTI-DIARRHEAL AND ANTI-DYSENTERIC ACTIVITY

Mamatha et al. (2014) reported that *E. thymifolia* showed improvement in patients suffering with diarrhea and dysentery.

53.3.8 ANTISPASMODIC ACTIVITY

E. thymifolia extract is found to have antispasmodic activity, which relieves the spasm and prevents further spasm occurrence. *E. thymifolia* methanolic extract could inhibit the growth of *Plasmodium falciparum* (Mon et al., 2008).

53.3.9 ANTIBACTERIAL

The EE of *E. thymifolia* screened against, *Bacillus pumilis, Staphylococcus aureus,* and *Bacillus subtilis*. EE showed significant antibacterial activity (Mon et al., 2008). Antibacterial activity of and chloroform (0.7 mg/ml),

EAE (0.45 mg/ml) extracts of *E. thymifolia* was tested against *Shigella flexneri* and *Escherichia coli*. Both extracts inhibited the growth of *S. flexneri* and *E. coli* while EAE extract was active only against *S. flexneri* (Khan et al., 1988).

53.3.10 ANTIMICROBIAL ACTIVITY

The alkaloids present in *E. thymifolia* exhibit significant antimicrobial activity (Khare, 2007). The standard six bacterial cultures viz., *Pseudomonas aeruginosa* ATCC-27858, *Bacillus subtilis* ATCC-6633, *Staphylococcus aureus* ATCC-25923, *Klebsiella pneumoniae* AYCC-10031, *Escherichia coli* ATCC-8739, *Salmonella typhi* and three fungal strains viz., *Candida albicans* ATCC-10231, *Penicillium chrysogenum, Aspergillus niger* ATCC-16404 were used for the antimicrobial activity. The fresh latex from *E. thymifolia* showed maximum activity when compared with dried latex, diluted latex, fresh juice and EAE, chloroform, butanol, extracts of fresh plant. Fluconazole and ciprofloxacin were used as standard drugs (Killedar et al., 2011).

53.3.11 ANTIBRONCHIAL ASTHMATIC ACTIVITY

E. thymifolia has beneficial role in the treatment of bronchial asthma, on the basis of experimental and clinical studies conducted by Sharma and Tripathi (1984) on the mixture of two plants, i.e., *E. prostrata* and *E. thymifolia* using of total alcoholic extract and a water-soluble fraction of the plants.

53.3.12 ANTHELMINTIC ACTIVITY

The methanolic and WEs of *E. thymifolia* were investigated against *Ascaridia galli* and *Pheretima posthuma*, and the extracts showed significant anthelmintic activity in a dose-dependent manner (Kane et al., 2009c).

53.3.13 LAXATIVE PROPERTY

Crude water extract of leaves of *E. thymifolia* given to rats produced significant laxative activity in a dose-dependent manner (Capasso et al., 1986). This laxative activity may be due to the presence of anthracene derivatives

in the leaves of *E. thymifolia* (Kane et al., 2009a). The crude EE is also used to study laxative activity. The results showed significant laxative activity in a dose-dependent manner (Kane et al., 2009b).

53.3.14 DIURETIC ACTIVITY

The crude EE and fractions of *E. thymifolia* showed significant diuretic activity in a dose-dependent manner (Kane et al., 2009a).

53.3.15 HEPATOPROTECTIVE ACTIVITY

The hepatoprotective activity along with antioxidant activity of *E. thymifolia* EE was determined. When the extract of *E. thymifolia* is given to rats before treating them with CCl_4, it showed to have hepatoprotective activity when CCl_4 is administered (Syed et al., 2011).

53.3.16 ANTI-ARTHRITIC ACTIVITY

To screen anti-arthritic activity, 22 Albino rats and aqueous extracts of *E. thymifolia* were used. A number of phytoconstituents were screened, and their effects in treating arthritis were measured using Freund's adjuvant. White blood cells, hemoglobin content, erythrocyte sedimentation rate, red blood cells, alkaline phosphate, total protein (TP), serum glutamic oxaloacetate transaminase, serum glutamic pyruvate transaminase, and LPO were estimated. This result proved the anti-arthritic activity of *E. hymifolia* (Gairola et al., 2013).

53.3.17 ANTI-STRESS ACTIVITY

Stress is one of the important factors in causing female reproductive dysfunction. Forced swimming stress and restraint stress are the major factors found to induce reproductive dysfunction (Sivaprasad et al., 2015a). Various concentration of the root extract of *E. thymifolia* is found to reduce the stress, which was observed by changes experienced during the estrous cycle and by the weight of the organs (Sivaprasad et al., 2015b).

KEYWORDS

- **antihyperglycemic activity**
- **antispasmodic activity**
- ***Euphorbia thymifolia***
- **hepatoprotective activity**
- **larvicidal activity**
- **laxative activity**

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CHAPTER 54

Phytochemical and Pharmacological Profile of *Euphorbia tirucalli* L. (Pencil Tree)

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54.1 INTRODUCTION

Euphorbia tirucalli L., which belongs to the family Euphorbiaceae, is a small tree widely distributed in semi-arid areas of tropical areas. The species is characterized with pencil-like branches, which have inspired its English name, the pencil tree. *E. tirucalli* is a flowering shrub or tiny tree which can grow up to 7–12 m tall and about 15–20 cm in stem width with straight twigs. It has smooth, cylindrical, terete, polished, whorled branchlets. Leaves alternate, sessile or sub-sessile, linear-oblong, cuneate at base, entire, obtuse at apex, 7–15×2–6 mm, fleshy, sparsely hirsute or glabrous. The flowers are small, yellow, green or pink arranged in groups on the terminal branches, discrete, and grouped at the top of the short branches, in heads, stalkless at the end of twigs, and carried in clusters at the apex of the short branches or in the angles of branches. Fruit is a capsule, about 8–12 mm in diameter, subglobose, glabrous, buff speckled with brown and with a dark brown ventral line (with a white line), around the small white caruncle 1 mm across.

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54.2 BIOACTIVES

E. tirucalli is reported to have euphol, β-sitosterol, euphorbol hexacosonate, cycloeuphordenol, cyclotirucanenol, tirucalicine, tri-methyl ellagic acid, gallic acids, terpenic alcohol, isoeuphorol, taraxasterol, tirucallol, euphorone, euphorcinol, euphorbins, 12-deoxy-4b-hydroxyphorbol-13-phenyl acetate-20-acetate, 12, 20-dideoxyphorbol-13-isobutyrate, glut-5-en-3-b-ol, 3,30-di-O-methylellagic acid, euphorbin-A (polyphenol), tirucallin-A (7) (tannin), tirucallin-B (11), euphorbin-F (14) (dimers), cycloartenol, 24-methylenecycloartenol, ingenol triacetate, 12-deoxy-4β-hydroxyphorbol-13-phenyl acetate-20-acetate, taraxerone, euphorginol, taraxerol, campesterol, stigmasterol, palmitic acid, linoleic acid, b-amyrin, etc., active phytoconstituents (Prashant et al., 2017).

Latex of *E. tirucalli* is vesicant and rubefacient, which is used for rheumatism, warts, cough, asthma, earache, toothache, and neuralgia. It acts as a purgative in small doses while in big doses it is bitter irritant and emetic. Latex is poisonous to rats and fish. Milky juice is acrid counter-irritant and emetic in large doses. Externally it is rubefacient (Nadkarni and Nadkarni, 2007). In Java, latex is used to heal skin ailments and bone fracture. In Malabar of India and Moluccas, the latex is used as an emetic and an anti-syphilitic. Oil obtained from latex was in the past used in linoleum, oil skin and leather cloth industry. Methane gas can be formed by anaerobic fermentation of latex (Duke, 1983). Milky juice is alexiteric, carminative, and purgative. It is useful in whooping cough, gonorrhea, asthma, leprosy, dropsy, dyspepsia, enlargement of spleen, colic, jaundice, and stone in the bladder. The fresh milky juice is a good alternative in syphilis and a good application in neuralgia. In Konkan, it is given as a purge (Kirtikar and Basu, 2006). In East Africa, latex is used against toothache, sexual impotence, hemorrhoids, epilepsy, snake bites, and cough (Van Damme, 1989; Gurib-Fakim, 2008).

54.3 PHARMACOLOGICAL ACTIVITIES

54.3.1 ANTIARTHRITIC ACTIVITY

The antiarthritic study of biopolymeric fraction (BET) of *E. tirucalli* was reported using adjuvant-induced arthritis model in rats by Sarang et al. (2007). BET-treated animal showed dose-dependent reduction in paw edema.

Administration of a dose of 400 mg/kg BET once daily up to 30 days did not show any noticeable unusual change or death.

54.3.2 ANTI-INFLAMMATORY ACTIVITY

Anti-inflammatory effect of euphol was checked by carrageenan-induced mechanical hyperalgesia at 30 and 100 mg/kg dose levels. The keratinocyte derived chemokine, IL-1b, IL-6 and tumor necrosis-a factor related to inhibition of myeloperoxidase (MPO) action were considered for further evaluation. Therefore, the outcome was substantiated to facilitate the euphol for managing inflammatory conditions (Dutra et al., 2012). Anti-inflammatory activity of petroleum ether, dichloromethane (DCM)-methanol, and aqueous extract of latex of *E. tirucalli* were evaluated by carrageenan-induced paw edema by Prabha et al. (2008). Ibuprofen was considered as standard drug. Results of the study revealed that petroleum ether, DCM-methanol, and aqueous extract showed considerable inhibition of inflammatory edema in rats at dosages 30, 100, and 300 mg/kg extracts, respectively.

54.3.3 ACTIVITY IN HUMAN-LYMPHOCYTES

The effects of 14 extracts from 70 plants of Euphorbiaceae were studied using prime immune cell culture by Doris et al. (2010). A peripheral blood mononuclear cell (PBMC) exposed to extract phyto-hemagglutinin-A or cycloheximide as agent with the intention to provoke proliferation in PBMC. 14 Euphorbiaceae extracts have been reported for their capability to transform at most 10 of the immune parameters. Latex extract of *Euphorbia cotinifolia* and *E. tirucalli* effectively induces uniformly proliferation and apoptosis in PBMC. Subfraction of *E. tirucalli* was reported for its ability to induce lymphocyte proliferation by without accessory cells.

54.3.4 ANALGESIC EFFECT

Analgesic potential of various extracts of latex of *E. tirucalli* was performed by using tail immersion and acetic acid induced writhing techniques. Percentage inhibition of aqueous, DCM-methanol, and petroleum ether extracts was 57.67%, 51.80%, and 48.48%, respectively. Treatment at

dosage 300 mg/kg of aqueous, 100 mg/kg of DCM-methanol and 30 mg/kg of petroleum ether extracts extensively decreases the number of writhes (Prabha et al., 2008).

54.3.5 ANTHELMINTIC PROPERTY

A study on anthelmintic activity of petroleum ether and DCM-ME of latex of *E. tirucalli* has been reported with 10 unusual concentrations (0.1%–1.0%) against *Pheretima posthuma* earthworm. The entire test group's exhibited decrease in time period to paralysis and death of earthworm in petroleum ether and DCM-MEs (Asha et al., 2009).

54.3.6 ANTIOXIDANT ACTIVITY

Antioxidant study of ME of 11 plants was investigated by DPPH, superoxide, hydroxyl radical, and reducing capacity. ME of all the plants exhibited potent antioxidant action (Chanda and Baravalia, 2010). Antioxidant effect of the aqueous extract of *E. tirucalli* has been studied using reducing capacity, superoxide anion, and hydroxyl radical scavenging assay (Jyothi et al., 2008). Hepatic damage was induced by CCl_4. The aqueous extract has shown dosage dependent antioxidant effect. Proteins were extracted from the laticifer cells of 30 plants. They have been examined for antioxidant potential using colorimetric methods. Acidic proteins have molecular masses of 12.5, and 74.5 kDa predominate in laticifers of *Plumeria rubra*, while *Conradina grandiflora* and *E. tirucalli* did not possess (Cleverson et al., 2010).

54.3.7 ANTIVIRAL POTENTIAL

Antiviral potential of petroleum ether and DCM-ME of *E. tirucalli* latex was investigated using tobamoviruses such as tobacco and tomato mosaic viruses by Ramesh et al. (2009). A concentration of extracts at 50, 100, and 150 ppm was used. Petroleum ether extract showed 80% defense in opposition to tomato mosaic virus at 150 ppm. The DCM-ME showed 81% defense against tobacco mosaic virus at 150 ppm. Lytic effect of herpes simplex virus (HSV-1) type-2 was performed by end-point titration technique. The water and ME of *Euphorbia cotinifolia* and *E. tirucalli* showed maximum action (Betancur-Galvis et al., 2002).

54.3.8 ANTIBACTERIAL/ANTIFUNGAL/ANTIMICROBIAL

Antimicrobial effect of petroleum ether and DCM-ME of latex of *E. tirucalli* was performed using *Bacillus subtilis*, *Klebsiella pneumoniae, Staphylococcus aureus*, and *Pseudomonas aeruginosa* by agar well diffusion assay. The aqueous extract was also tested against *Aspergillus niger*, *Penicillium chrysogenum*, *Trichoderma viride*, and *Candida albicans* by agar well diffusion assay. Zone of reduction was determined for bacteria at 5%, 10%, 15% and 20% and for fungi at 3%, 6%, 9% and 12% concentrations. *B. subtilis* was resistant to tested extracts (Prabha et al., 2008). Antibacterial and antifungal effect of methanol, chloroform, n-hexane, and aqueous extracts from *Sapindus emarginatus*, *Hibiscus rosa-sinensis, Mirabilis jalapa*, *E. tirucalli*, *Vitex negundo* and *Saussurea lappa* against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus epidermidis* bacterial strains and *Aspergillus flavus*, *Candida albicans*, and *C. glabrata* fungal strains using agar diffusion and agar tube dilution assays. The result of these studies reports zone reduction by n-hexane extract of *E. tirucalli* at concentration 100 mg/mL (Rathi and Patel, 2012). Antimicrobial potential of acetone, chloroform, hexane, petroleum ether, and MEs of stem of *E. tirucalli* was performed using *Bacillus megaterium*, *B. subtilis*, *E. coli*, *Enterococcus faecalis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus niger*, *Aspergillus fumigatus* and *Candida albicans*. Acetone extract is reported for inhibition in the direction of all micro-organisms. *E. coli* was found to be very sensitive to acetone extract. Chloroform extract (CE) was reported as an active extract against *Bacillus subtilis*, *E. coli*, *P. vulgaris*, *S. aureus*, *A. niger*, and *C. albicans*. ME was reported as an active extract against *Bacillus subtilis*, *E. coli*, *Enterococcus faecalis*, *S. aureus*, and *C. albicans*. Petroleum ether and hexane extract did not show any activity (Swapna and Prasad, 2012). Antimicrobial potential of crude alcoholic extract of leaf and stem of *E. tirucalli* against the different microbial strains such as *E. coli*, *P. vulgaris*, *S. enteritidis*, *B. subtilis*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *C. albicans*, *C. tropicalis*, *Aspergillus niger*, *A. fumigatus*, *A. flavus*, and *Fusarium oxysporum* by disc diffusion method has been reported. *E. coli* and *P. aeruginosa*, *Klebsiella pneumoniae*, and *S. aureus* were responsive to leaf extract. Stem extract exhibited considerable antimicrobial potential in opposition to *P. vulgaris* and *K. pneumoniae* (Bhuvaneshwar et al., 2010). Antimicrobial potential of methanolic, acetone, ethyl acetate (EAE), water, and gemmo-modified extract of *Terminalia arjuna* and *E. tirucalli* was evaluated by disc diffusion technique by Nazish et al. (2008). Bacterial strains viz. *B. subtilis,*

S. aureus, *E. coli*, *Pasteurella multocida* and fungal strains viz. *Rhizoctonia solani* and *A. niger* were used. The methanolic extract of *E. tirucalli* was reported for maximum outcome against *S. aureus* and *B. subtilis* at 1,000 µg concentration. Gemmo-modified extract of *E. tirucalli* was more efficient in opposition to *E. coli.* Antimicrobial potential of ME of 11 plants against eight microorganisms by agar well diffusion method was investigated. The ME has showed the highest activity with gram-positive bacteria and fungi. *E. tirucalli* have shown the best antimicrobial activity (Chanda and Baravalia, 2010).

54.3.9 CYTOTOXICITY/ANTICANCER ACTIVITY

Anticancer activity of euphol was studied using human gastric cancer cells. Elevated cytotoxicity was shown by euphol in human gastric CS12 cancer cells than non-cancer CSN cells. Anti-proliferative effect of euphol was due to the improved p27kip1 and decreasing cyclin B1 levels. The inhibitions of ERK1/2 activation through PD98059 upturned euphol induce pro-apoptotic protein expression and cell death. Therefore, euphol selectively induces apoptosis of gastric cancer cells by means of modulation of ERK signaling, which might be useful in cancer treatment (Lin et al., 2012).

E. tirucalli unpurified latex was studied by MacNeil et al. (2003) for Epstein–Barr virus gene expression. Different dilutions of latex were used as a treatment in Burkitt lymphoma cell line. It was reported that latex was able to reactivate the Epstein–Barr virus lytic cycle in a dose dependent mode. Latex treated with protein kinase C inhibitor was blocked cycle activation.

54.3.10 GENOTOXIC/MUTAGENIC EFFECT

Aveloz latex and phytotherapic solutions were prepared from *E. tirucalli* and evaluated for their genotoxic and mutagenic effect by induc, ames, and chromo test. A result of induc test showed no decrease in bacterial survival and increase in lysogenic cycle. Ames and chromo test did not show mutagenic or genotoxic effects (Juliana et al., 2011).

54.3.11 HEPATOPROTECTIVE ACTIVITY

Aqueous extract of *E. tirucalli* was tested against CCl_4-induced hepatic damage in rats by Jyothi et al. (2008). The extract produced considerable hepatoprotective activity by decrease in levels of serum bilirubin, cholesterol,

triglycerides, and tissue lipid peroxidation (LPO). GSH level in tissue was increased.

54.3.12 IMMUNOMODULATORY ACTIVITY

Immunomodulatory study of BET of *E. tirucalli* was evaluated by Sarang et al. (2007) for delayed-type hypersensitivity, leukocyte migration, vascular permeability, lymphocyte immune phenotyping and IL-2 and IFN-g BET. Significant decreases (25.0%–28.2%) DTH response, dose dependent reduction of total leucocytes count, and vascular permeability was observed. Production of TNF-a, IFN-g, and IL-4, IL-10 cytokines were evaluated using crude latex *of E. tirucalli.* Result showed significant increase in percentage of $CD4^+$ T lymphocytes which was positive for TNF-a, IFN-g, and IL-10 (Bethania et al., 2011).

54.3.13 LARVICIDAL EFFECT

Larvicidal effect of petroleum ether, EAE and butanol extract of *Jatropha curcas*, *Pedilanthus tithymaloides*, *Phyllanthus amarus*, *Euphorbia hirta* and *E. tirucalli* were studied by Rahuman et al. (2008) using 4^{th} in star larvae of *Aedes aegypti* and *Culex quinquefasciatus*. Low larvicidal effects were shown by the extracts. Larvicidal efficiency of *E. tirucalli* latex was studied using *Anopheles fenestus* and *Anopheles gambae* by Mwine et al. (2010). Latex showed total mortality with the highest dilution 1: 250 at 5 days. LT-50 and 90 was 12 and 36 h for the same dilution.

54.3.14 MYELOPOIESIS EFFECT

Myelo suppression effect was studied by Marize et al. (2006) by increased number of spleens CFU-GM in tumor-bearing mice. *E. tirucalli* extract stimulated narrow myelopoiesis and reduced spleen colony formation in treated animals. Therefore, the extract appreciably improved survival and reduced tumor growth.

54.3.15 PROTEOLYTIC/CHITINOLYTICS

Proteins were extracted from laticifer cells of *Plumeria rubra*, *Conradina grandiflora*, and *Euphorbia tirucalli* and examined in respect of proteolytic and chitinolytic effects by zymography and colorimetric assays. The acidic

proteins were not predominated in laticifers of *E. tirucalli*, while chitinase action was predominated (Cleverson et al., 2010).

KEYWORDS

- **antiarthritic activity**
- **biopolymeric fraction**
- **cytotoxicity**
- ***Euphorbia tirucalli***
- **hepatoprotective activity**
- **latex**

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CHAPTER 55

Phytochemical and Pharmacological Properties of *Excoecaria agallocha* L.

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55.1 INTRODUCTION

Excoecaria agallocha L. is a small, non-viviparous, and milky mangrove species that grows widely in tidal forests and belongs to the Euphorbiaceae family. This plant is found in the countries of temperate and tropical Asia, Australasia, and the South-western Pacific (Aleman et al., 2010). It has a stilt type rooting system and can be cultivated as ornamental. This plant species has anti-HIV, anticancer, antibacterial, and antiviral properties. Its bark oil is effective against rheumatism, leprosy, and paralysis (Bandaranayake et al., 2002; Patra, 2012). Traditionally, this species is used to treat sores, ulcers, leprosy, etc. (Ghani, 2003). The toxic latex of this species is the source of many larvicidal and insecticidal products, especially mosquito repellent (Thirunavukkarasu et al., 2011).

55.2 BIOACTIVES

Chemical screening revealed the presence of diterpenoids (like ribenol, stachenol, agallochaone A, excolides A, B, etc.), flavonoids (afzelin, (+)-catechin, luteolin, myricetin, quercetin, etc.), Phenolic acids (ellagic acid, gallic acid, vanillic acid), tannins (corilagin, furosin, tercatain, etc.), sterols (β-sitostenone, β-sitosterol, etc.), triterpenoids (betulin, epilupeol,

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taraxerol, etc.) from *Excoecaria agallocha* (Chan et al., 2018). Leaves, stem, latex, and root part have different types of polyphenols, terpenoids, and volatile derivatives. Again, leaf part has enormous number of compounds like diterpenoids, triterpenoids, flavonoids, alkaloids, anthraquinone, phytosterol, fixed oil, phorbole esters, free amino acids, mucilage, glycosides, carbohydrates, and lignin (Kaliamurthi and Selvaraj, 2016; Zou et al., 2006; Deepa and Padmaja, 2014). Alcohols like exocarol, agalocol, isoagalocol, mannitol, etc., are present in latex of this species, while seeds contain alkaloids, carboxylic acid, flavonoids, phenol, saponin, resins, steroids, tannin, and sugars showing anti-inflammatory and analgesic activity (Babuselvam et al., 2012). Structures of some compounds are given in Figure 55.1.

55.3 PHARMACOLOGY

55.3.1 ANTIVIRAL ACTIVITY

Isolates of *E. agallocha* leaves and stems have a novel phorbol ester (12-deoxyphorbol-13-deca-3, 5-dienoate), which can have capacity to inhibit HIV-1 replication *in vitro* condition (Erickson et al., 1995). The ethanol leaf extract of *E. agallocha* also has potent activity against HIV (Premanathan et al., 1996). Ethanolic stem fraction of *E. agallocha* also can inhibit the reverse transcriptase (RT) enzyme and prevents the synthesis of proviral DNA (Patil et al., 2011). Isolates from the wood of *E. agallocha* (diterpenoids) can inhibit Epstein-Barr virus (EBV) (Konoshima et al., 2001; Konishi et al., 1998). Phenolic contents of *E. agallocha* leaves (excoecariphenol D and corilagin) can inhibit hepatitis C virus (HCV) (Li et al., 2012).

55.3.2 ANTIBACTERIAL ACTIVITY

Fresh leaf samples of *E. agallocha* have higher antibacterial activity against *Enterobacter* species, *Staphylococcus aureus,* and minimum inhibitory was observed in *Proteus* sp. and *Salmonella typhi*. Dried leaf samples of *E. agallocha* show maximum antibacterial activity against *S. typhi, Vibrio cholerae* followed by *S. aureus*. Fresh root samples of *E. agallocha* have maximum antibacterial activity against *S. typhi*, *Enterobacter*, *Proteus*, *Vibrio cholerae*

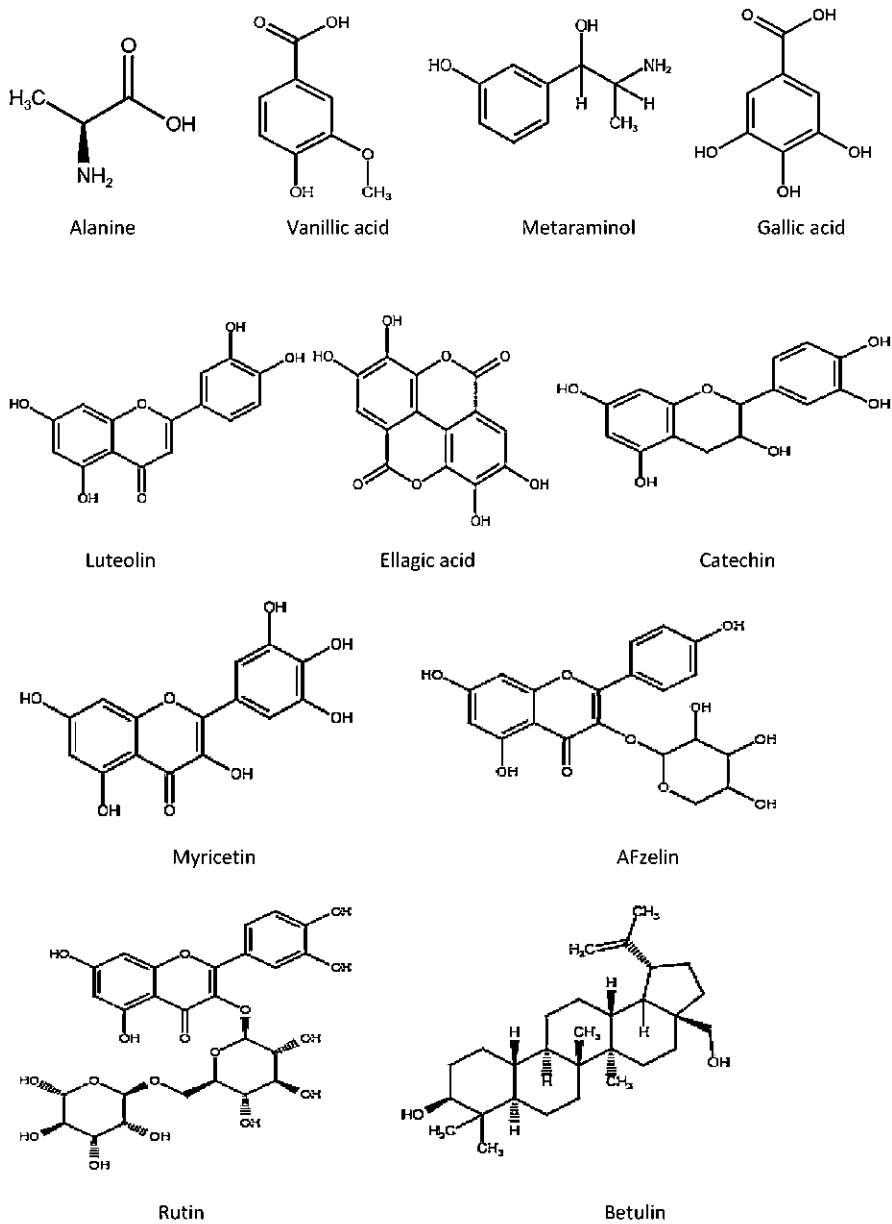


FIGURE 55.1 Some bioactive phytochemicals of *E. agallocha* species.

in the agar well method. Dried root samples of *E. agallocha* ethanol extract has a higher antibacterial activity for *S. aureus*. Fresh stem samples of *E. agallocha* ethanol extract has higher antibacterial activity for *Enterobacter*, and *Vibrio cholerae*. The extracts have higher activity for *Proteus* sp. and *V. cholera*. The ethanol extract of the sample has higher activity against *S. aureus* and *Proteus.* Dried stem samples of *E. agallocha* have maximum higher antibacterial activity against *Proteus* sp., *Vibrio cholerae*, *Staphylococcus aureus* followed by *Salmonella typhi* and *Enterobacter* species (Prakash and Sivakumar, 2013). In *Excoecaria agallocha,* dried plant samples have higher inhibitory capacity than fresh plant extracts against the pathogenic bacteria (Prakash and Sivkumar, 2013).

55.3.3 ANTIFUNGAL ACTIVITY

Antifungal activity of inferred that, ME of *E. agallocha* exhibited 100% antifungal activity against *C. albicans* (Kumar et al., 2011); while chloroform and acetone extracts of *E. agallocha* exhibited comparatively less antifungal activity. *E. agallocha* leaves extract have antifungal activity against *R. solani, Fusarium udum, M. phaseolina,* and *Sclerotium rosii* (Kumar and John, 2013).

55.3.4 ANTIHYPERGLYCEMIC EFFECT

The stem extract of *E. agallocha* have antihyperglycemic activity and have potential sources of antidiabetic drugs (Rahman et al., 2010). Ethanolic extract (EE) of leaves of *E. agallocha* has significant hypoglycemic activity in diabetic mice. This is due to the presence of flavonoids, tri-terpenoids, alkaloids, and phenolics bioactive compounds (Thirumurugan et al., 2010).

55.3.5 ANTIMALARIAL AND ANTI-ULCER ACTIVITY

The ethanolic leaf extract of *Excoecaria agallocha* show *in vitro* antiplasmodial activity especially against *Plasmodium falciparum* (Ravikumar et al., 2011). The bark extract of *E. agallocha* can reduce the acidity and also can increase mucosal defense of gastric areas. So, it can be used as an antiulcerogenic agent (Thirunavukkarasu et al., 2009).

55.3.6 ANTIFILARIA AND ANTI-INFLAMMATORY ACTIVITY

E. agallocha is also a source of agents which can block embryogenesis in filarial parasites and can be used against lymphatic filariasis in human beings. The organic solvent extracts of leaves of the plant proved as potent anti-filarial (Patra et al., 2009; Alok et al., 2009). *E. agallocha* leaf extract has anti-inflammatory property by showing membrane stabilizing effect and protect of the erythrocyte against its lysis (Rahman et al., 2016).

55.3.7 ANTIOXIDANT AND FREE RADICAL SCAVENGING EFFICIENCY

The extract of *E. agallocha* shows antioxidant properties due to the presence of phytochemicals like phenols, flavonoids, etc. (Sofia and Teresa, 2016). *Excoecaria agallocha* can be a potential source of agent that can be used not only for meeting the oxidative stress (Patra et al., 2009). The hydroalcoholic extract of *E. agallocha* shows significant 2,2-diphenyl-1-picrylhydrazyl, hydrogen peroxide, and nitric oxide (NO) and free radical scavenging activity, respectively. Lower concentration of alkaloid rich fractions of *E. agallocha* has significant DPPH free radical scavenging activity (Subhan et al., 2008b; Satyavani et al., 2013). The solvent extracts of leaves of the plant proved as potent antioxidant (Alok et al., 2009).

55.3.8 CANCER THERAPY

Both methanol and chloroform leaf extracts of *E. agallocha* are cytotoxic against Hep-2 cancer cells (Batsa and Periyasamy, 2013). While ethanol stems extract of *E. agallocha* have cytotoxic effects on certain pancreatic cancer cells (Patil et al., 2011).

55.3.9 ANALGESIC AND OTHER ACTIVITY

E. agallocha possesses analgesic properties by inhibiting prostaglandin synthesis as well as central inhibitory mechanisms (Subhan et al., 2008a). The extract of *E. agallocha* can be used as therapeutics and contains nephron-protective, hepatoprotective, and cardioprotective agents (Kiran et al., 2018).

KEYWORDS

- **antifungal activity**
- **antiviral activity**
- **Epstein-Barr virus**
- ***Excoecaria agallocha***
- **hepatitis C virus**
- **pharmacology**

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CHAPTER 56

Biomolecules and Therapeutics of *Flueggea leucopyrus* Willd. [Syn.: *Securinega leucopyrus* (Willd.) Müll.-Arg.]

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56.1 INTRODUCTION

The importance of herbal plants for their medicinal properties is always acknowledged by developing countries like India, Sri Lanka, Burma, etc. *Flueggea leucopyrus* Willd. [Syn.: *Securinega leucopyrus* (Willd) Müll. Arg.] is one of such plants which has noticeable value in cultural heritage as well as in traditional medicinal uses (Gopal, 2013). This plant belongs to the family Euphorbiaceae. *Flueggea leucopyrus* is also known as Thumri in Sanskrit, Pandharfali in Marathi, Humari in Hindi, Shinavi in Gujarat, and Spinous fluggea in English. This bushy weed commonly grows in desert area of India, Sri Lanka and Burma. Male plant is identified as yellow colored cluster leaves while female plant appears in red leaves. White color berry like fruits is a characteristic of a plant. According to Britto (1998), traditionally tribal people from Sri Lanka, Shaurastra, Southern parts of Asia, Australia, and Malaysia were using this plant as a medicine. Since many years, tribes from Sri Lanka were efficiently treating various skin diseases, seminal defects and physical weakness using this valuable medicine (Matthew, 1981). Ethnobotanical importance of this plant was also reported by Donda et al. (2013) and Jayaweera (1980) in curing cough, hay asthma, bowel complaints, disinfections, laxatives for diarrhea, gonorrhea, constipation, mental illness, and kidney stones. *F. leucopyrus* is a major source of bergenin, which is a

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vital chemical compound in many drugs (Wijayabandara et al., 2015). In the present review, bioactive compounds and medicinally important properties from spinous fluggea are reviewed.

56.2 BIOACTIVES

According to Vajira and Amila (2014), methanolic and aqueous extracts of leaves and bark of *F. leucopyrus* showed the presence of alkaloids, terpenoids, unsaturated sterols, glycosides, saponins, phenolics, flavonoids, tannins, carbohydrates, and protein. Methanolic extracts of leaves and bark exhibited 0.13% of alkaloids, 0.74% of saponins, and 1.15% of tannins, and 0.02%, 0.19%, and 1.62%, respectively. Total phenolics were quantified from aqueous and methanolic extracts of leaves and bark as 34.86 mg/g, 3.98 mg/g, 38.49 mg/g, and 29.93 mg/g in gallic acid, respectively. Compared with the standard quercetin, flavonoids were calculated as 20.33 mg/g, 11.86 mg/g, 11.48 mg/g, and 6.42 mg/g from both aqueous and methanolic extracts of leaves and bark. Amount of carbohydrates and proteins were measured as 48.73% and 53.07% (leaves and bark) and 21.20% and 12.87% (leaves and the bark). Hettihewa et al. (2015) found bergenin as a biologically active compound (isomers E and H) from spinous fluggea plant. This compound is characterized as C glucoside of 4-O-methyl gallic acid. Ethanolic extract (EE) of leaves of *F. leucopyrus* showed presence of 9-Octadecenoic ACID (Z) (20.547), l-(+)-Ascorbic acid 2,6-dihexadecanoate (22.030), Heptadecanoic (23.09), 9-Octadecenoic acid, methyl ester, (E) (23.550), 9,12-Octadecadienoic acid (Z,Z) (25.042), Oleic Acid (Octadec-9-enoic acid) (26.800) (Rajeswari and Muthuirulappan, 2015) (Figure 56.1).

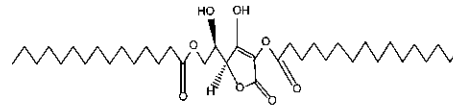
56.3 PHARMACOLOGY

56.3.1 ANTIOXIDANT ACTIVITY

Antioxidant property of spinous Fluggea was revealed (Vidyadhar et al., 2010) using chloroform extract (CE) of aerial parts of the plant. Considerable antioxidant activity of extract was reported, which was compared with standard vitamin E. Gopal (2013) extracted aerial parts of spinous fluggea in chloroform, ethyl acetate (EAE), alcohol, hydro alcohol and hexane. It was reported that except hexane all other extracts showed dose dependent enhancement in DPPH and nitric oxide (NO) scavenging activity. Around 82.5% and 88.42% DPPH scavenging activity was noticed for chloroform and alcoholic extracts. DPPH radical scavenging, NO radical scavenging



Tetradecanoic acid



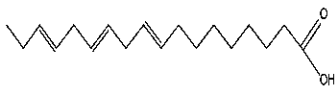
l-(+)-Ascorbic acid 2,6- dihexadecanoate



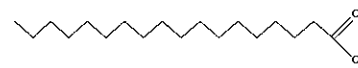
Heptadecanoic acid



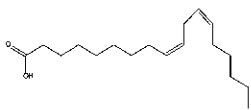
9-Octadecenoic acid, methyl ester, (E)



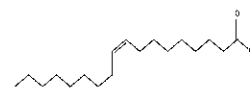
9,12,15- Octadecatrienoic acid



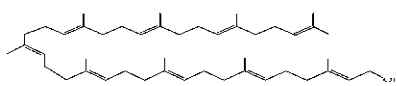
Octadecanoic acid



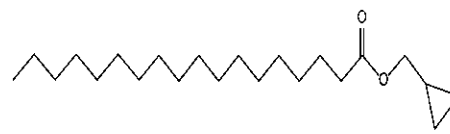
9,12-Octadecadienoic acid (z,z)



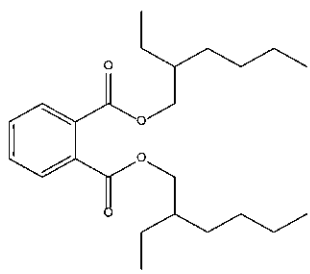
9- Octadecenoic (Oleic Acid)



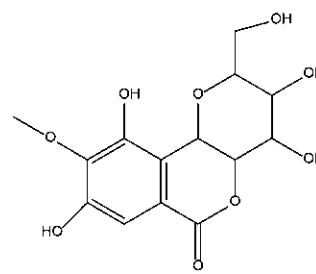
Solanesol



Glycidyl stearate



bis(2-ethylhexyl) phthalate



3,4,4a,10b-Tetrahydro-3,4,8,10-tetrahydroxy-2-(hydroxymethyl)-9-methoxypyrano[3,2-c][2]benzopyran-6(2H)-one

FIGURE 56.1 Bioactive compounds from leaf of *Flueggea leucopyrus* (Rajeswari and Muthuirulappan, 2015).

activity and 2-deoxy-D-ribose degradation assays were performed to evaluate antioxidant property of aqueous leaves extract of *F. leucopyrus* on HEp-2 cells (Soysa et al., 2014). DPPH radical scavenging, NO radical scavenging activity and 2-deoxy-D-ribose degradation exhibited EC_{50} values as 11.16±0.37, 4.82±1.82, and 23.77±3.16 μg/mL, respectively. At the same time, the experiment of MTT and LDH showed EC_{50} values as 506.8±63.16 and 254.52±42.92 μg/mL, respectively.

56.3.2 ANTIBACTERIAL ACTIVITY

Trimurti et al. (2016) reported that methanolic fruit extract of *F. leucopyrus* was effective against inhibition of growth of 25 bacterial species, 56 strains of 24 bacterial species. Very strong growth preventing activity of extract was observed against species of genera belonging to *Acinetobacter, Bacillus, Brevundimonas, Brucella, Enterobacter, Escherichia, Micrococcus, Pseudomonas, Staphylococcus,* and *Xanthomonas*. Methanolic extracts of both leaf and stem bark of spinous fluggea were noticed to be effective against preventing bacterial growth of 8 bacterial strains (4 positive and 4 negative). At the highest concentration of extracts (250 μg/ml), prominent antibacterial activity was reported (Dudhamal et al., 2020). Variation in antibacterial activity from high to low of aqueous leaf extract of *F. leucopyrus* was observed by Helina et al. (2015). Noteworthy antibacterial activity of leaf extract was observed against *Klebsiella pneumoniae* (1.55), *Escherichia coli* (1.35), *Streptococcus mutans* (1.1), *Pseudomonas aeruginosa* (1.1), and *Bacillus cereus* (0.95). Growth of *Salmonella typhi* (0.85) and *Serratia marcescens* (0.8) was moderately affected. At the same time, low inhibition zone was observed in *Proteus mirabilis* (0.7) and *Vibrio cholerae* (0.55). Variation in antibacterial activity of aqueous and methanolic extracts of spinous flueggea was noticed (Fernando et al., 2014). They found that aqueous extract was prominent against bacteria than methanolic. Aqueous extract exhibited antibacterial activity against *Escherichia coli* NCTC 10418, *Pseudomonas aeruginosa* NCTC 10662, *Staphylococcus aureus* NCTC 6571, *Staphylococcus aureus* ATCC 25923, and *Staphylococcus aureus* (MRSA) however extract was not effective against *A. tumefaciens*.

56.3.3 ANTIFUNGAL ACTIVITY

Methanolic extracts of leaf and bark of spinous fluggea showed prevention of *Aspergillus flavus* growth at the concentration of 250 μg/ml (Dudhamal

et al., 2020). Growth of *Candida albicans* and *Candida tropicalis* fungi was totally inhibited by hydro-alcoholic leaf extract of *F. leucopyrus* (Helina et al., 2015).

56.3.4 WOUND HEALING ACTIVITY

Exogenous application of paste, made with spinous fluggea in sesame oil had recovered chronic wound in diabetic patient within 15 days (Dudhamal and Ajmeer, 2015). Ghodela and Dudhamal (2017) reported that topical application of Thumari gel prepared using Sesame oil, leaves of *F. leucopyrus* and leaves and stem of *F. leucopyrus* in ratio (1: 4: 16) caused healing of chronic ulcer in 45 years patient. Effectiveness of Thumari gel was similarly observed by Ghodela and Dudhamal (2018). Bed sores created due to hemiparesis were treated successfully with local application of a gel. They stated that this recovery was due to enhancement in fibroblast activity, new blood vessel formation and rapid collagen accumulation. Regular application of *F. leucopyrus* leaves paste caused the formation of new connective tissue and microscopic blood vessels in the skin, which were affected due to infection of *Staphylococcus aureus* (Ajmeer et al., 2014). Skin ulcers present on the left foot of a 62-year-old male patient was treated effectively with daily application of spinous fluggea gel (Kapadiya and Dudhamal, 2019).

56.3.5 ANTICANCEROUS ACTIVITY

Methanolic and aqueous extracts of aerial parts of *F. leucopyrus* were tested for their antitumor property. For this experiment carrot disc assay and Cisplatin, Vincristin as standards were employed. On carrot disc, total inhibition of cancerous cells was observed due to standards. At the same time, 90% prevention of tumorous growth was observed at (10,000–1,250 ppm) concentrations of plant extracts (Fernando et al., 2014). Aqueous extract of aerial parts of *F. leucopyrus* was tested by Mendis et al. (2015) against three breast cancer cell phenotypes (MCF-7, SKBR-3, and MDA-MB-231). It was observed that, Her2 negative cell lines (MCF-7 and MDA-MB-231) were more affected due to extract than Her2 positive cell line SKBR-3. The authors also noticed that extract had not caused any cytotoxic effect on the non-cancerous breast cell line MCF-10A. Leaves and bark of spinous fluggea were extracted in methanol, aqueous, and EAE solvents to check their anticancerous property. For this test, Brine shrimp cytotoxicity assay was performed. Along with this, anticancerous nature of a plant was tested

using MTS cell proliferation and HTERT inhibitory assay. Aqueous and methanolic extracts of bark and leaves exhibited IC_{50} values for Brine shrimp normal cell lethality assays as 400.64 µg/ml, 2058.34 µg/ml, 2779.63 µg/ml, and 8567.35 µg/ml, respectively. MTS cell proliferation was declined due to compounds E and H which were isolated from methanolic bark and EAE leaves extracts. Promising decline in HTERT was observed due to compound H (50–200 µg/m, p) (Hettihewa et al., 2015).

56.3.6 DIURETIC ACTIVITY

Diuretic activity of *F. leucopyrus* was first time reported by Ellepola et al. (2015). They noted that aqueous extract of a whole plant had the capacity to increase urine output in hydrated rats. Treatment of extract had caused instant electrolyte absorption and smooth passage of them which gave appropriate results. They suggested that plant extract has high potassium level which restricts kidney tubules to absorb excess amount of potassium, and which ultimately results in increase in urine output.

56.3.7 LARVICIDAL ACTIVITY

Extracts of *F. leucopyrus* prepared in hexane, chloroform, and EAE were found to be effective against III instar larvae of *Earias vittella*. Noticeable antifeedant activity (81%) was reported at 5% concentration of hexane. At this same concentration of hexane extract maximum larvicidal activity was also noticed (Muthu et al., 2012).

56.3.8 ANTHELMINTIC ACTIVITY

Deepika et al. (2018) noticed that aqueous extract of aerial parts of spinous fluggea was effective against earthworms. Various concentrations of this extract caused paralysis in earthworms. They concluded that alkaloids present in the extract are responsible for this anthelmintic activity. Similarly, Sambandan and Dhatchanamoorthy (2012) reported that worms were successfully destroyed by using leaf paste of *F. leucopyrus* and tobacco.

56.3.9 NOOTROPIC ACTIVITY

Alcoholic flower extract of spinous fluggea was used to study nootropic activity in mice. For this experiment, mice were treated with Diazepam and

Scopolamine to induce amnesia. Behavioral changes in mice after treatment with extract were compared with the standard drug Piracetam. Enhancement in inflection ratio was noticed in Piracetam and extract given mice. Authors opined that phytochemicals like glycosides and flavonoids present in extract are responsible for this change (Sheikh et al., 2014).

56.3.10 APHRODISIAC ACTIVITY

Effect of ethanolic leaf extract of *F. leucopyrus* on the aphrodisiac activity of mice was studied (Usnale and Biyani, 2018). For this study, 200 and 400 mg/kg body weight concentrations of extract were orally given at regular intervals of 15th, 30th, and 45th day to the animals. It was reported that both the concentrations of extract were positively worked on improving intromission latency, mounting frequency, and ejaculatory latency. At the same time, these concentrations caused a decline in intromission latency, mounting latency, inter-intromission interval, and post-ejaculatory interval. A noticeable increase in main and accessory reproductive organs weight and sperm motility was also reported.

ACKNOWLEDGEMENT

Author would like thank her guide Dr. P.D. Chavan for his valuable inputs. Author is also thankful to her Principal and Head of Department of Botany for providing facilities to complete this review.

KEYWORDS

- **antioxidant property**
- **diuretic activity**
- **Euphorbiaceae**
- ***Flueggea leucopyrus***
- **pharmacology**
- ***Securinega leucopyrus***

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CHAPTER 57

Bioactives and Pharmacology of *Mallotus philippensis* Müell.-Arg.

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57.1 INTRODUCTION

The genus *Mallotus,* included in the Euphorbiaceae family, comprises about 124 species distributed mainly in hot and flourishing environments of the World, and India consists of around 20 species (Gangwar et al., 2014). *Mallotus philippensis* (Lam.) Müell.-Arg. is widely distributed in hot and flourished forests of peripheral regions of the Himalayan regions with an altitude below 1,000 m. It is well known medicinal plant of Asia and Australia with popularly called the Kamala tree, monkey-faced tree (English), Kamala, Sindur, Rohini, Kambhal (Hindi), Kumkumamu (Telugu), Kinbil (Arabic), Kanbela (Pers), Rora (Santhal), etc. (Gangwar et al., 2014; Kumar et al. 2021).

Mallotus philippensis is a medium-sized to large monoecious tree, up to 25 m tall. Branchlets are reddish-brown glandular, leaves alternate, simple, more or less leathery, ovate to lanceolate, base cuneate to rounded with two

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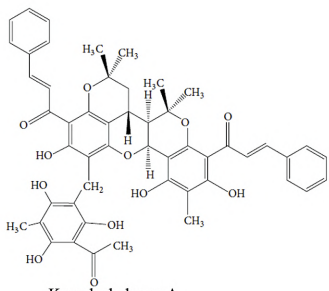
foliar glands at base; leaf apex acute or acuminate, midveins 3, prominent, reddish glandular hairs present on the lower surface. Inflorescence panicle, axillary, and terminal position. Flowers yellow with red spots, unisexual, 2–10 cm long, solitary or fascicled paniculated spikes, numerous small stamens; female flowers found on slender racemes, stellate hairy, ovary tricarpellary syncarpous, stigmas-3, papillose. Fruit capsule, trilobed, covered with reddish or orange color glandular granules, seeds-3, black in color.

The plant is used in Ayurveda for cooling and appetizer, glandular hairs of the capsules used as purgative, to reduce overheat, carminative, and anthelmintic. It is also useful to abdominal diseases, enlargement of the spleen and bronchial asthma (Usmanghani et al., 1997). In Sanskrit, *Mallotus* is known as Kampillakah/Kamala, is used as an oral drug for birth control. Further, it is also used to treat parasitic infections related skin diseases such as herpes, scabies, and ringworm. In traditional medicine the plant is used to destroy filarial worms (Singh et al., 1997). Scientifically the plant was reported for various pharmacological properties like anti-inflammatory, immune regulatory, anthelmintic, antibacterial, and antiparasitic (Gangwar et al., 2014). Kumar et al. (2021) reviewed the phytochemistry and pharmacology of *Mallotus philippensis*.

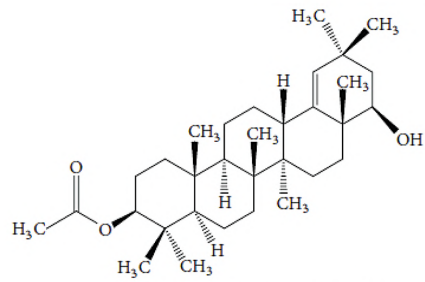
57.2 BIOACTIVES (PHYTOCHEMICALS)

This plant is known for its chemical diversity, because it consists various types of secondary metabolites such as terpenes (di and triterpenoids), steroids, flavonoids, coumarinolignoids, cardenolides, coumarin, isocoumarins. One of the major chemical constituents of *M. philippensis* is rottlerin (Gangwar et al., 2014). *M. philippensis* seeds contain a poisonous glycoside and about 20% fixed oil from which and kamlolenic acids (18-hydroxy-9,11,13-octadecatrienoic acids) were isolated by Gupta et al. (1952). Tanaka et al. (1998) elucidated and characterized the phytochemicals like Dimeric chalcone derivative Kamalachalcone A and B from *M. philippensis.* Some of the important constituents of Kampillaka are as follows: acetylaleuritolic acid, cortotoxigenin, α-amyrin, coroglaucigenin, sitosterol, octacosanol, β-sitosterol, glycoside, bergenin rottlerin, isoallorottlerin, isorottlerin, kamalin, wax, kamalin, homorottlerin phorbic acid, gum, bergenin, citric, and oxalic acids, tanins, volatile oil (Sharma et al., 2002).

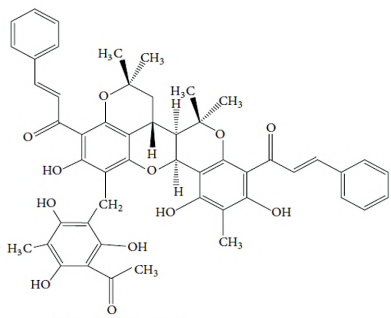
Furusawa et al. (2005) characterized one new flavanone, 4′-hydroxyisorottlerin along with six known chemical compounds from this plant. Shradha et al. (2007) determined various phenolic compounds and authenticated the crude drug samples collected from different places of India by subjecting them to HPLC analysis using standard phenolic compounds (tannic acid, gallic acid, caffeic acid, vanillic acid, ferulic acid, chlorogenic acid, cinnamic acid, para coumaric acid, oxalic acid and salicylic acid) from fruits. A new lignan dimer, bilariciresinol, was isolated from the leaves of *M. philippensis*, along with platanoside, isovitexin, dihydromyricetin, bergenin, 4-*O*-galloylbergenin, and pachysandiol A (Mai et al., 2010).



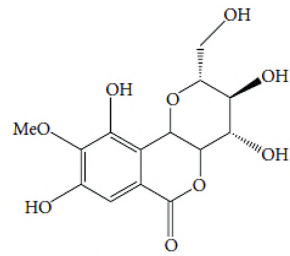
Kamalachalcone A



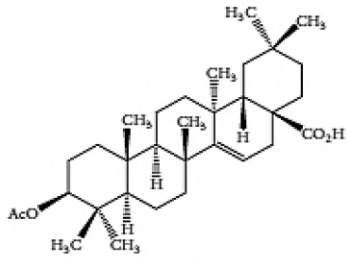
3b-Acetoxy-22b-hydroxyloean-18-ene



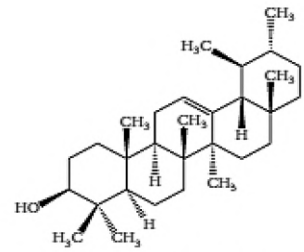
Kamalachalcone B



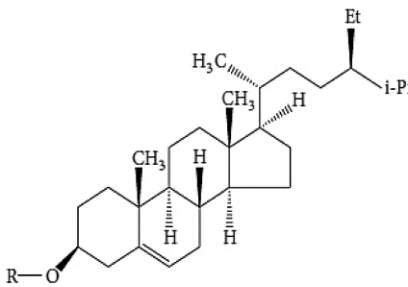
Berginin



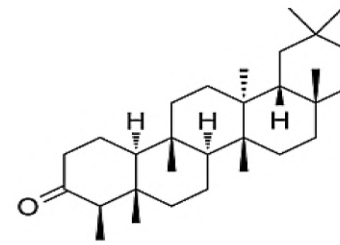
Acetylaleuritolic acid



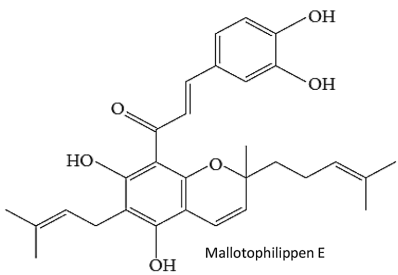
alfa - Amyrin



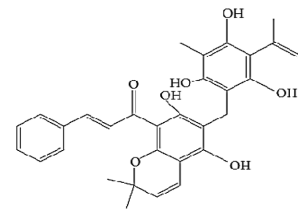
Beta sitosterol



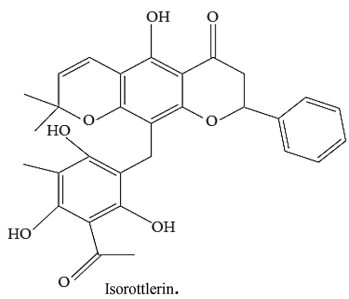
Friedelin



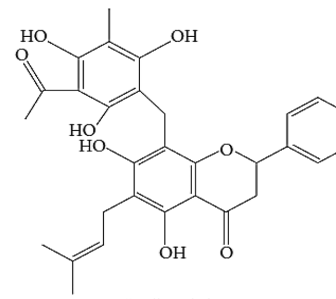
Mallotophilippen E



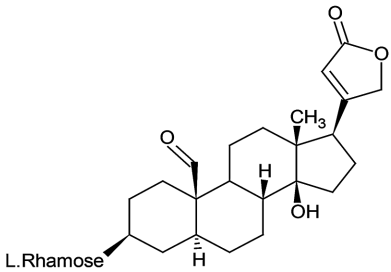
Rottlerin



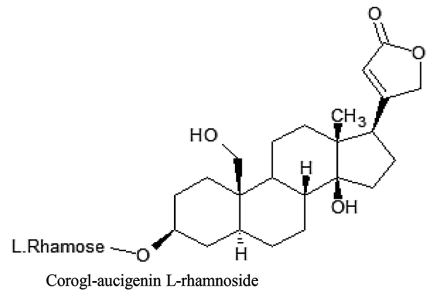
Isorottlerin.



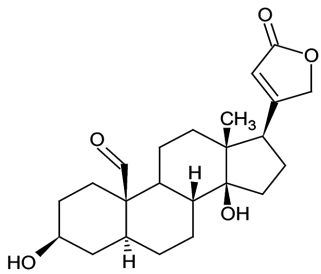
Isoallorottlerin



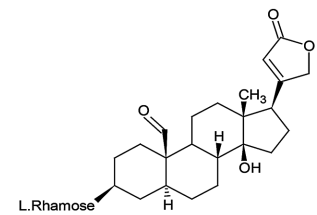
Coroglaucigenin



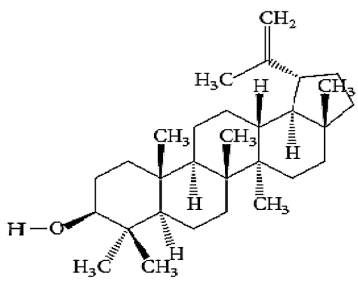
Corogl-aucigenin L-rhamnoside



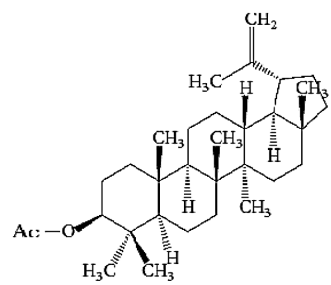
Corotoxigenin



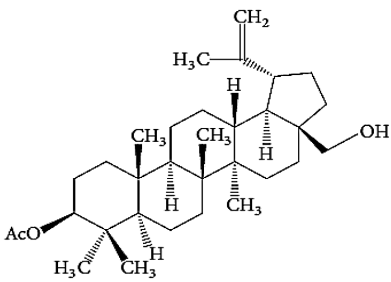
Corotoxigenin L-rhamnoside



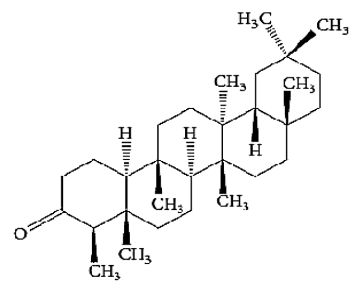
Lupeol



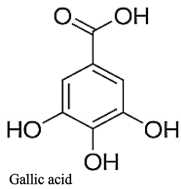
Lupeol Acetate

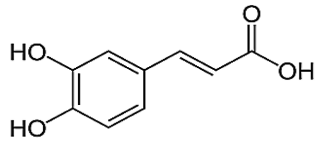


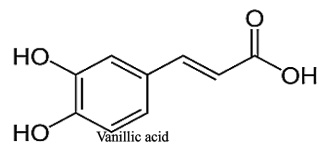
Betulin-3-acetate.

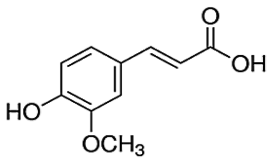


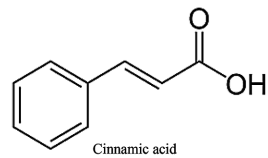
Friedelin

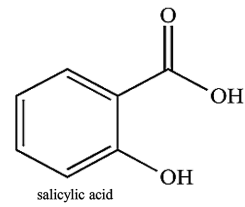

Gallic acid

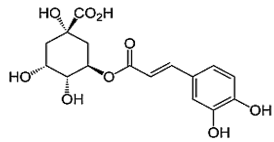

Caffeic acid

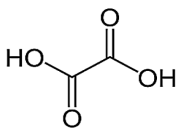

Vanillic acid

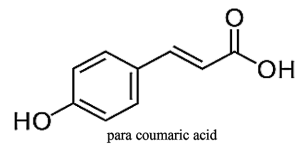

Ferulic acid

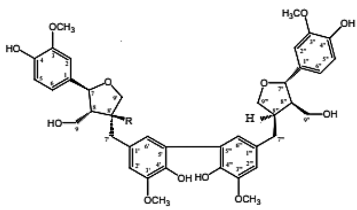

Cinnamic acid

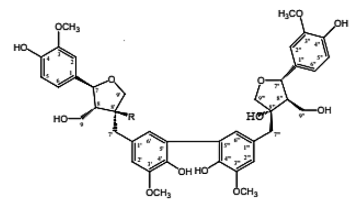

salicylic acid

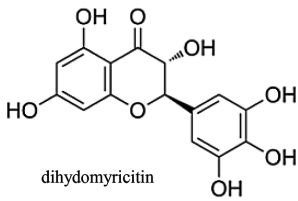

Chlorogenic acid

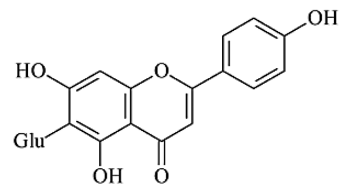

Oxalic acid


para coumaric acid


Bilariciresinol

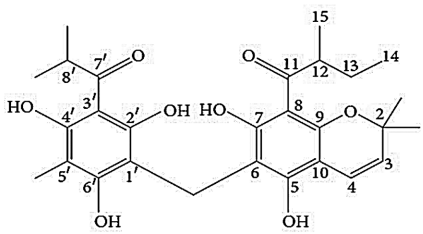

Platanoside


dihydomyricitin

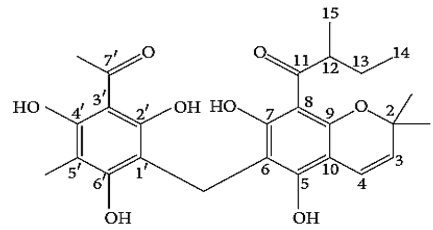

Isovitexin

57.3 PHARMACOLOGY

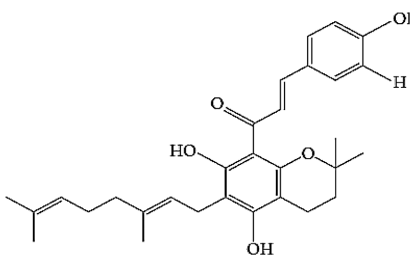
57.3.1 ANTIVIRAL ACTIVITY



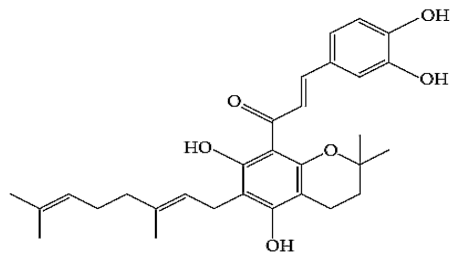
Mallatophilippen A



Mallotophilippen B



Mallotophilippen C



Mallotophilippen D

Inhibitory activity of four chemical constituents of phloroglucinol derivatives such as mallotophenone, mallotolerin, mallotojaponin, and mallaotochromene on HIV-reverse transcriptase (RT) was investigated. It revealed that, of the tested four components, two, i.e., mallotojaponin, and mallaotochromene suppressed the enzyme activity 70% at 10 µg/ml concentrations under reaction conditions. The other two constituents exhibited very feeble activity (Nakane et al., 1991).

57.3.2 ANTIMICROBIAL ACTIVITY

The antimicrobial activity of *M. philippensis* stem extracts in hexane, chloroform, and ethanol showed in dose dependent. The ethanol extract showed antimicrobial activity against the fungi *Aspergillus flavus* and *Candida albicans* (Jayaraman et al., 2011; Afzal et al., 2013; Bhakshu and Raju, 2014; Madhavi, 2015). Antibacterial activity along with preliminary phytochemical screening of fruit extracts, was studied by Gangwar et al. (2011), stating its

potential antibacterial activity. Rottlerin and 8-cinnamoyl-5,7-dihydroxy-2,2,6-trimethylchromene (red component) exhibited noteworthy inhibitory activities against several clinically isolated and antibiotic-resistant bacterial strains, including methicillin-resistant *Staphylococcus aureus.* But no reports on the antibacterial effects of these components were noticed against gram-negative bacterial strains.

Nevertheless, red compound and rottlerin showed noteworthy inhibition of transfer of plasmids such as pUB307, TP114, R6K, and pKM101 conjugated with *E. coli* at 100 mg/ml concentration. Interestingly, despite the planar nature of the compounds, binding to plasmid DNA could not be demonstrated by a DNA electrophoretic mobility shift assay. The results indicated that these two components have potential antibacterial activity, may lead to develop antibacterial drug. It requires further studies to elucidate the mode of action behind its activity (Oyedemi et al., 2016).

Antibacterial activity of *M. philippensis* fruit extract at different concentrations was evaluated using *in vitro* by well diffusion method against pathogenic microbes such as *Pseudomonas aeruginosa, Yersinia pestis, E. coli* and *Staphylococcus aureus.* The results revealed that, among the tested extracts acetone and MEs strongly inhibited *P. aeruginosa* wound infecting microbe (Shelly et al., 2016).

Antimicrobial activity using bacterial and fungal strain with various chemical fractions (Hexane, chloroform, ethyl acetate (EAE), n-butanolic, and aqueous fractions from the bark) of leaf of *M. philippensis* effectively inhibited the growth of seven human pathogens *viz. Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Serratia marcescens*, *Bacillus subtilis* and *Micrococcus luteus* (Bigyan et al., 2017). Cheenpracha et al. (2019) isolated antibacterial phenolic components from *M philippensis* fruits.

57.3.3 ANTI-TUBERCULOSIS

Five chemical constituents isolated from *M. philippensis* using bioassay-guided fractionation method. Of the isolated components, mallotophilippen-F, a new compound, strongly inhibited *Mycobacterium tuberculosis.* The novel natural chromene compound, 8-cinnamoyl-2,2-dimethyl-7-hydroxy-5-methoxychromene, was isolated from kamala dye a natural resource for the first time, while the three compounds, rottlerin, iso-allorottlerin (isorottlerin) and the "red compound," 8-cinnamoyl-5,7-dihydroxy-2,2,6-trimethylchromene,

had been characterized from this plant and proved as an anti-tuberculosis medicament (Hong et al., 2010).

57.3.4 ANTIOXIDANT ACTIVITY

Several extracts obtained from *M. philippensis* fruits and bark were evaluated for their DPPH scavenging potential, reducing power capacity and to estimate total antioxidant activity capacity. The bark extract exhibited the highest DPPH-reducing activity and reduction power with its TAA (5.27 mmol Trolox equivalents/g) (Arfan et al., 2006). Antioxidant activity of phenolic fractions of *M. philippensis* bark extract (Arfan et al., 2009) were determined using *in vitro* assays for the phenolic fractions with special reference to Berginin.

The antioxidant capacity of rottlerin, a phenolic component isolated from *M. philippensis* fruits, was assessed against oxalate/calcium oxalate-induced oxidative stress in rat models. It revealed that rats treated with rottlerin at 1 mg/kg/day along with the hyperoxaluric agent significantly reduced oxalate/calcium oxalate-induced oxidative stress. Further, it significantly reduced hyperoxaluria-induced renal damage, quenched free radicals, and interrupted signaling molecules involved in stone formation (Chhiber et al., 2016).

57.3.5 HEPATOPROTECTIVE ACTIVITY

The Wistar rats were pre-treated with the ME of leaf, exhibited significant protective role against CCl_4 induced hepatotoxic and the represented through down regulation of elevated levels of liver biomarkers such as SALP, SGPT, SGOT, bilirubins, and the malondialdehyde (MDA). The histological organization of rat liver tissues are reversed by the extracts at 100–200 mg/kg, in the CCl_4-induced hepatic damage as compared with the standard such as silymarin. In addition, the extracts proved as effective liver tonic as it improved the hepatocyte functionality besides its effective antioxidant capacity (Ramakrishna et al., 2011).

57.3.6 ANTIUROLITHIATIC ACTIVITY

Antiurolithiatic activity of alcoholic leaf extract of *M. philippensis* was assessed against ethylene glycol-induced urolithiasis in Wistar rats. The

calcium, oxalate, and phosphate concentration were significantly increased in disease control animals as compared to the normal control animals. However, the tested extracts (250 and 500 mg/kg) and standard cystone (750 mg/kg) significantly reduced calcium, oxalate, and phosphate concentration in urine as compared to disease control animals (Patel et al., 2020).

57.3.7 ANTI-INFLAMMATORY AND IMMUNOREGULATORY ACTIVITY

The phloroglucinols were reported for the effective inhibition of nitric oxide in the activated macrophage cells and the chalcones such as mallotophilippens C, D, and E, inhibit nitric oxide (NO) production and the expression of NO synthase (iNOS gene) in RAW 264.7 (murine macrophage-like cell line), The cells were activated in presence of bacterial toxin such as lipopolysaccharide (LPS) and mouse interferon-gamma (recombinant IFN-gamma). Further studies suggested that genes such as cyclooxygenase-2 (COX-2), interleukin-1b and interleukin-6 were expressed the down trend regulation. The reports indicated that the tested chalcones have a significant role in anti-inflammatory and immune modulation properties (Daikonya et al., 2002, 2004).

57.3.8 WOUND HEALING ACTIVITY

The bark extracts of *M. philippensis* were reported for the peculiar migration of stem cells (mesenchymal) and improved the healing of wound in the tested mice. The ethanol extract of the bark proved effective performance on the multiplication, movement towards the wound site, and its healing in the tested models *in vitro* (mesenchymal stem cell) as well as *in vivo* (mouse) systems (Furumoto et al., 2014). *M. philippensis* fruit extract found as nontoxic and effective in the wound healing process and it also involved in the reduction of free radicals developed during the damage of tissue besides promoting the status of antioxidants and enhancing the collagen production were reported by providing strong support from histopathological studies (Gangwar et al., 2015).

The phytochemical components such as [5,7-dihydroxy-2,2-dimethyl-6-(2,4,6-trihydroxy-3-methyl-5-acetylbenzyl)-8-cinnamoyl-1,2-chromene] and the red compound (8-cinnamoyl-5,7-dihydroxy-2,2,6-trimethyl-chromene) obtained during the guided isolation and characterized and

evaluated its efficacy on the antibiotic-resistant bacterial strain of *E. coli* with inhibition effect on the plasmid binding studies (Oyedemi et al., 2016).

57.3.9 ANTIALLERGIC ACTIVITY

The antiallergic effect of rottlerin and phloroglucinol compounds of Kamala dye tree effective in the studied models such as mouse and guinea pig contraction of bronchial rings and rottlerin has been demonstrated for the prevention of IgE-related processes such as "cutaneous vascular extravasation," hypothermia, maintained of histamine in plasma, mast cell degranulation, etc. (Daikonya et al., 2002, 2004). Chan et al. (2013) proved that rottlerin effected the Ig-E-related secretion of β-hexosaminidase from the tested mast cells and its cascade found beneficial in the treatment of asthma and allergic ailments (Chan et al., 2013).

57.3.10 ANTIDIABETIC ACTIVITY

The ethanol extract of the fruits of Kamala dye tree significantly effective on the management of diabetes reported in the streptozotocin (STZ) induced mice model. The extracts exhibited significant antidiabetic effect along with the diabetic-related pathological markers such as TC, glycated hemoglobin, and serum markers antioxidant (enzymatic or non-enzymatic) status besides the enhancement of plasma insulin levels clearly demonstrated for its efficacy on the maintenance of diabetes and its complications (Shabeer and Sumithira, 2016).

57.3.11 ANTICANCER ACTIVITY

Cancer treatment involves the chemotherapy which affects the cancer cells through autophagy, or apoptosis and preventing the invasion or migration of cancer cells and these were significantly demonstrated with Rottlerin (Maioli et al., 2012a).

Rottlerin, has been incontestable as an efficient chemoprevention agent in inhibiting neoplasm cell growth. Studies on the overexpression of Skp2 abrogated the anti-tumor perform evoked by rottlerin in carcinoma cells. Systematically, depletion of Skp2 promoted rottlerin-mediated inhibition of cell growth and invasion. It's incontestable that rottlerin might suppress Skp2

expression and after exerting its neoplasm restrictive effective in carcinoma cells, suggesting that rottlerin can be a possible therapeutic compound for treating carcinoma (Su et al., 2016).

Rottlerin also effectively inhibited breast cancer cell proliferation and controlled the expression or inactivation of Skp2 levels which suggested to play a prominent role as a potential therapeutic agent (Yin et al., 2016). Ma et al. (2018) have reported that rottlerin, a natural polyphenolic compound from the mature fruits of *M. philippensis*, possessed the anticancer role on diverse cell lines and rottlerin has been suggested as a potential medicament in cancer treatment. The molecular mechanism of antitumor effectiveness of rottlerin has demonstrated in different malignant carcinomas such as non-small cell lung cancer (NSCLC) by Zhao et al. (2017). Shi et al. (2018) reported that rottlerin suppressed cell growth, triggered cell necrobiosis and elicited cell cycle arrest. Additionally, rottlerin restrained cell migration and invasion in malignant hepatoma (HCC) cells. The results incontestable that rottlerin exerted its antiproliferation activity partially through the inhibition of TAZ (transcriptional co-activator with PDZ-binding motif). Additionally, the depletion of TAZ concluding to restrained cell growth and invasion, whereas the overexpression of TAZ increased cell growth and invasion within the HCC cells. Taken along, these findings indicated that the inhibition of TAZ by rottlerin is also a unique strategy for treating HCC.

57.3.11.1 Anti-Leukemic Activity

The root extract (hexane fraction) of *M. philippensis* was reported for inhibitory effect on leukemia and HL-60 multiplication of cells which was coincidingly showed apoptosis and toxicity along with the effectiveness on the cell cycle regulation proteins (Khan et al., 2013).

57.3.11.2 Kinase Protein Inhibitor

Further the effect of rottlerin demonstrated on the protein kinase activity and calcium and potassium channels significantly and other events in the mitochondrial activities were studied by Soltoff (2007) and inferred that, rottlerin effected by downregulation of PKC-δ (Gschwendt et al., 1994; Soltoff, 2001, 2007) in addition to suppression of proliferation and metastasis of cancer cells (Choi et al., 2001, 2009). The effect of rottlerin on glioma cells and colon carcinoma to “tumor necrosis factor (TNF) related apoptosis

inducing ligand" modulated the apoptosis (Tapia et al., 2006; Lim et al., 2009). It has recently been proposed that rottlerin could provide therapeutic benefits for malignant glioma cells when used in combination with another chemotherapeutic. For example, rottlerin sensitized colon carcinoma and glioma cells to TRAIL (TNF-related apoptosis-inducing ligand)-mediated apoptosis via mitochondrial uncoupling and inhibition of Cdc2, respectively (Tapia et al., 2006; Lim et al., 2009). The natural polyphenols were used in traditional medicines and got attention on the natural compounds such as curcumin and whereas rottlerin got less attention and recently it was found as a selective inhibitor of PKCδ as comparable to curcumin. These two molecules modulating the expression of DNA methyltransferase, heme oxygenase, cyclooxygenase (COX), lipoxygenase (LOX) and NF-kB and STAT transcription factors and inhibiting the aggregation of precursors of amyloid proteins besides its anti-inflammatory and antioxidant benefits in many human ailments (Maioli et al., 2012b).

57.3.12 EFFECT ON PSORIASIS

The strong scientific rationale combined with the relative safety of rottlerin suggests that it has the potential to be developed as a new, potent, and nontoxic agent for treating psoriasis. The main component of *M. philippensis*, rottlerin, showed antioxidant, antiproliferative, antiangiogenic, and anti-inflammatory which have linked each other through NFkB in a cause-effect relationship. Rottlerin indeed is a potent and "universal" inhibitor of the redox-sensitive transcription factor NFB. The antioxidant activity of rottlerin, along with its inhibitory action on signaling molecules are likely responsible for NFB inhibition, which in turn, through inhibition of cell proliferation and inflammation, is expected to alleviate the skin damage caused by psoriasis, which also prevent binding of cytokines following their secretion by T cells before they can act on keratinocytes to drive the formation of psoriatic plaques, interfere with pathways responsible for the expression of cytokines (e.g., blockage of interferon or ILs receptors (Valacchi et al., 2009; Maioli and Valacchi, 2010).

57.3.13 EFFECT ON PARKINSON'S DISEASE (PD)

Rottlerin demonstrated as a protector of neuronal cells of mesencepahalic cell isolated from the black mice. The tested cells were pretreated with the

rottlerin which prevented the MPTP-induced neuronal problems and found that the post-treatment also determined the neuronal protective effective in Parkinson's disease. The protective role of rottlerin proved for the mechanism involving through the inhibition of protein kinase (PKC-δ) and this effect also resulted significant protective role in animal model, inferring its usage in Parkinson's disease (Zhang et al., 2007).

57.3.14 ANTI-HELMINTHIC ACTIVITY

The leaf extracts of kamala dye tree exhibited a potential inhibition of the motility of whole worm – microfilaria larvae (*Setaria cervi*) using *in vitro* and exhibited whole worm paralysis effect (Singh et al., 1997). The clinical study was performed on school children for the intestinal parasites, i.e., round warm, hookworm, and giardia which were frequent in children. The consumption of *M. philippensis* has reported fairly good results. The combination with *Embelia ribes* and *Butea monosperma* found effective on cysticercoids stage on the mature feeding stage for four days treatment (Sharma and Varma, 2011). The ME of fruits exhibited a significant effect on the cestodal infections and the protoscoleces (*Echinococcus granulosus*) in viability determined in the *in vitro* model with the standard such as Praziquantel (Gangwar et al., 2013).

57.3.15 ANTI-FERTILITY ACTIVITY

An ethereal extract of *M. philippensis* seed is reported to have an antifertility effect in female rats when mated with normal males, and the positive pregnancy rate was decreased along with the implantations. The results of the investigation of Thakur et al. (2005) inferred that hormonal changes such as decreased follicle stimulating hormone and Luteinizing hormone levels, number, and quality of eggs, estrous cycle, etc., were affected and leading to infertility condition.

57.4 CONCLUSION

The medicinal and pharmacological effects of *M. philippensis* and its parts were effective in the maintenance, and curative properties of different human ailments were systematically studied by the scientific community around the

World. Besides, the extracts were found as nontoxic at the recommended doses requires further detailed analysis for the improvement as a medicament for regular treatments.

KEYWORDS

- **anti-fertility activity**
- **kamala**
- **lipoxygenase**
- ***Mallotus philippensis***
- **rottlerin**
- **tumor necrosis factor**

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CHAPTER 58

Bioactives and Pharmacology of *Phyllanthus amarus* Schum. & Thonn.

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58.1 INTRODUCTION

Phyllanthus amarus Schum. & Thonn. (*Phyllanthus niruri* auct non L. and sensu Indian authors*) is an herb and it has been used as traditional medicine since 1000 BC. *P. amararus,* of Phyllanthaceae family, is an herbaceous plant, commonly known as Black catnip, Child pick-a-back, Shatterstone, Gulf leaf flower, gala of wind, Stone breaker (English); Bhoomyaamlakee, Bhoodha-tree, Tamalakee (Sanskrit), Nelavusiri, Nelavusirika (Telugu), Bhumi amla, Jangli amli (Hindi), Keelanelli (Tamil), Nela-nelli, and Kirunelli (Kanada). It is an erect herb up to 60 cm height, smooth, phyllanthoid branches look like compound leaf; flowers trimerous, unisexual, and axillary, males' flowers towards apex of the branch and females towards base of the phyllanthoid branch; fruit 6-lobed, 6-seeded. Seeds are trigonous shaped with 5–6 ribs on the back. *P. amarus* is widely distributed tropics and sub-tropics.

This species was defined to have the properties of Guna, Rasa, Veerya, and Vipaaka. In Ayurveda, it was said to use as Shwaasahara (antidyspnoic, antispasmodic), Kaphapittahara (Kapha Pitta Dosha reliever), Kaasahara (antitussive), Raktapittahara (hemorrhage), Pipaasaaghna (Polydipsia reliever), Kaamalaahara (jaundice), relieves from burning sensation), Mootrarogahara (cures urinary disorders), Kshatakshayaghna (indicated in Trauma), Kushthaghna (leprosy), and Paanduhara (anti-anemic).

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Taxonomic issue: *Phyllanthus amarus* is wrongly called *P. niruri* L. in India, actual (*P. niruri* is restricted to South America and recently introduced N. America too). So called *Phyllanthus niruri* from India and its related publications are to be considered as *P. amarus* only. Morphologically as similar as *P. amarus* is *P. fraternus* (number of tepals 6).

P. amarus works as anti-inflammatory, anti-carcinogenic, hepatoprotective, anti-bacterial, anti-viral, and more activities (Jay Ram et al., 2011). It has many activities against health disorders because it has major bioactive compounds classes; flavonoids, alkaloids, sterols, tannins, lignans, volatile oils, and triterpenes which all are isolated from the plant. Phyllanthin and hypophyllanthin lignans; quercetin, a flavonoid, were isolated from leaf powder. All *Phyllanthus* species are medicinally important, and this group of plants is treated as raw herbal drugs in India (Jay Ram et al., 2011).

58.2 BIOACTIVES

P. amarus has many secondary metabolites; some of them are lignans, which are major flavonoids, hydrolyzable tannins (ellagitannins), triterpenes, alkaloids, sterols, volatile oil, and polyphenols. The main active constituents of *P. amarus* are lignans in which phyllanthin (a bitter constituent), hypophyllanthin (a non-bitter constituent), niranthine, nirurin, nirtetralin, phyltetralin, etc., are different chemicals. The maximum quantities of hypophyllanthin (0.3% w/w), and phyllanthin (0.7% w/w) have been stated in leaves while, in the stem, these two are minor in their amounts (Sharma et al., 1993). Lignans which were separated from *P. amarus* are niranthin, phyltetralin, isonirtetralin, lintetralin, isolintetralin, 5-demethoxyniranthin, hypophyllanthin, phyllanthin, nirtetralin, hinokinin, demethylenedioxy-niranthin, etc. (Morton, 1981; Chevallier, 2000; Huang et al., 2003; Kassuya et al., 2006; Srivastava et al., 2008; Maciel et al., 2007; Singh et al., 2009).

Flavonoids in which quercetin-3-O-glucopyranoside, phyllanthusiin, quercetrin, rutin, gallocatechin, kaempferol 3-D-glucopyranoside, etc., are different types (Foo and Wong, 1992; Foo, 1993a; Londhe et al., 2008; Morton, 1981; Jay Ram et al., 2011). Ellagitannins (hydrolyzable tannins) include furosin, amariin, geraniin, geraniinic acid B, amariinic acid, amarulone, repandusinic acid A, isocorilagin, corilagin, elaeocarpusin, phyllanthin D gallic acid, phyllanthin A, B, C, D, repandusinic acid A and melatonin (Foo and Wong, 1992; Foo, 1993a, 1995). Triterpenes are phyllanthenol, phyllanthenone, phytllantheol, etc. (Maciel et al., 2007; Foo and

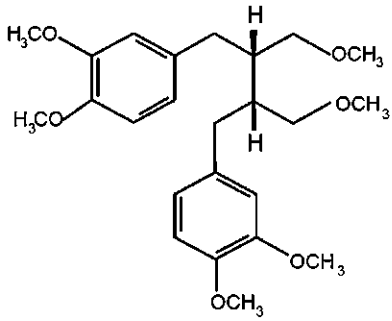
Wong, 1992). Alkaloids are many in which securinine, dihydrosecurinine, tetrahydrosecurinine, securinol, phyllanthine, allosecurine, nor-securinine, epibubbialine, isobubbialine, 4-methoxy dihydrosecurinine, 4-Methoxytetrahydro-securinine, 4-hydrosecurinine, etc. are main compounds (Houghton et al., 1996; Kassuya et al., 2006; Foo and Wong, 1992); isobubbialine and epibubbialine are securinega-type alkaloids. Sterol such as amarosterol-A, amarosterol-B, etc. (Ahmad and Alam, 2003) and volatile oils such as linalool, phytol, etc. (Moronkola et al., 2009; Foo and Wong, 1992; Foo, 1993a; Londhe et al., 2008; Morton, 1981) were also reported, Hamrapurkar et al. (2010) optimized a method for isolation and characterization of phyllanthin.

The oils from *P. amarus* were analyzed for its ingredients by gas chromatography (GC), and GC together with MS (mass spectrometry) (GC/MS) (Moronkola et al., 2009). Result outcome from the study of oil reveals that 82 chemical compounds were identified which are responsible for 87.6% of the oil content of *P. amarus*. The oil was dominated with linalool (36.4%) and phytol (13.0%). Other significant compounds were hexahydrofarnesyl acetone (3.4%), pentacosane (2.5%), naphthalene (2.4%), (E)-b-ionone (2.3%), nonacosane (2.1%), tetracosane, and octacosane (ca. 1.7%). Eight among all components were in trace amount (they are less than 0.1%). The classes of compounds present in *P. amarus* oil are monoterpene hydrocarbons (0.2%), oxygenated monoterpenoids (11.0%), sesquiterpene hydrocarbons (1.3%), oxygenated sesquiterpenoids (3.3%), diterpenoids (8.5%), aliphatic alcohols (51.2%), fatty acids (3.9%), aldehydes (8.0%), ketones (0.5%) and esters (0.3%) (Moronkola et al., 2009). Two new lignans which are: (1) 3-(3,4-dimethoxy-benzyl)-4-(7-methoxy-benzo[1,3]dioxol-5-yl-methyl)-dihydrofuran-2-one; and (2) 4-(3,4-dimethoxy-phenyl)-1-(7-methoxy-benzo[1,3]dioxol-5-yl)-2,3-bis-methoxymethyl-butan-1-ol were isolated from the leaves of *P. amarus* (Singh et al., 2009). Phytochemical exploration of methanolic extract revealed the occurrence of six bio-active lignans [isolintetralin (2,3-demethoxy-seco-isolintetralin diacetate), demethylene-dioxy-niranthin, 5-demethoxy-niranthin, niranthin, phyllanthin, and hypophyllanthin] and one triterpene 2Z, 6Z, 10Z, 14E, 18E, 22E-farnesyl farnesol (Maciel et al., 2007). Phytochemical assessment of *P. amarus* showed to contain high level of saponins and tannins at 24.05 and 17.50%, respectively, but with low content of cyanogenic glycosides (1.46%). The potassium (K) and sodium (Na) substances were high at 150.30 mg and 228.20 mg per 100 g dry weight, respectively; while magnesium (Mg), calcium (Ca), iron (Fe), and phosphorus (P) were all low at 2.40, 1.60, 1.65, and 1.00 mg per

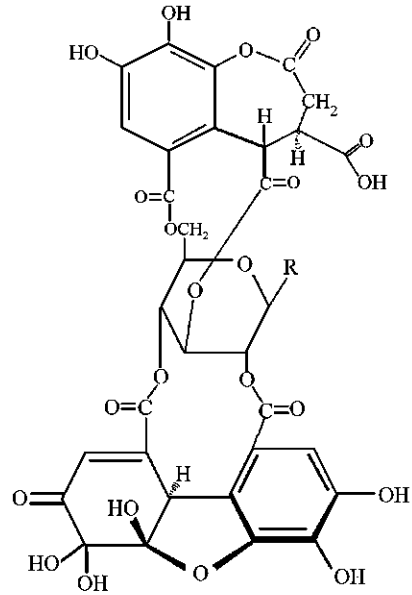
100 g dry weight, respectively (Igwe et al., 2007). The rough extract of phyllanthin was obtained from *P. amarus* using solvents of varied polarity. The presence of pyrrolizidine type of alkaloids was reported in the extract of *P. amarus.* These are securinine, dihydrosecurinine, tetrahydrosecurine, securinol-B, phyllanthine, allosecurine, nor-securinine, etc. (Kassuya et al., 2006). *P. amarus* has afforded new secosterols named as amarosterol-A characterized as 13, 14-seco-stigma 5(6), 14(15)-diene-3-ol and amarosterol-B characterized as 13, 14-seco-stigma 9(11), 14(15)-diene-3-ol (Ahmad and Alam, 2003). Highest concentration of polyphenols was observed in *P. amarus* (George et al., 2001). Alkaloids isobubbialine, epibubbialine phyllanthine, securinine, and nor-securinine were isolated from *P. amarus* leaves (Houghton et al., 1996). Arial parts of *P. amarus* examinations with polar extractives led to the isolation of a novel ellagitannin, amariinic acid along with 1-O-galloyl-2, 4-ehydrohexahydroxydiphenoyl-glucopyranose, elaeocarpusin, repandusinic acid A and geraniinic acid B. Amarulone was isolated from *P. amarus* (Foo, 1993a). A new hydrolyzable tannin amariin along with corilagin, geraniin, 1,6-digalloylglucopyranoside, quercetin-3-O-glucopyranoside and rutin were isolated and identified from the polar fractions of *P. amarus* plant. The amariin tannin structure was recognized as 1-galloyl-2, 4: 3,6-bis-dehydrohexahydroxydiphenoylglucopyranoside in which the cyclohexenetrione portion of the dehydrohexahydroxydiphenoyl moieties were linked to the O-3 and O-4 of the glucose moiety (Foo, 1993b). Ellagitannin, phyllanthusiin D was isolated and its structure was established as 1-galloyl-2, 4-(acetonyl-dehydrohexahydroxydiphenoyl)-3, 6-hexahydroxydiphenoyl-glucopyranoside (Foo and Wong, 1992) from *P. amarus*.

58.3 PHARMACOLOGY

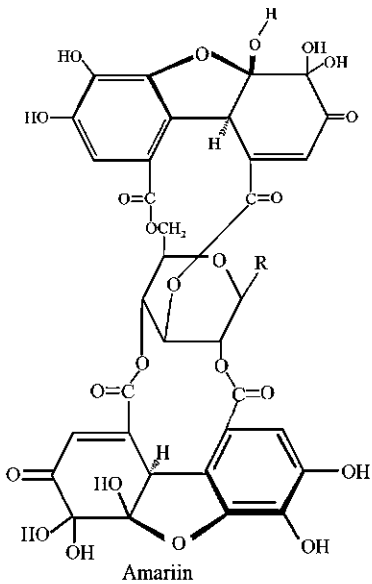
The use of *Phyllanthus amarus* is first in the race because of its enormous antiviral activity on hepatitis B and many other biological activities like removal of gallbladder stones, kidney stones, and flu, cold, tuberculosis, and other viral infections (Jay Ram et al., 2011). Liver diseases and disorders plus jaundice, hepatitis, and liver cancer (Unander et al., 1993). *P. amarus* is bitter, antiseptic, febrifuge, astringent, diuretic, and stomachic. It also works to improve the immunity of patients by boosting liver function and acts against liver cell toxicity, and it is very effective against hepatitis A (Jayram et al., 1997). *P. amarus* has been used for curing various disorders,



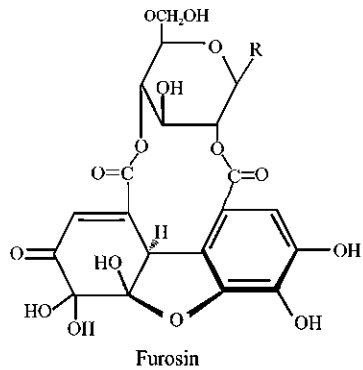
Structure of phyllanthin



Amarulone



Amariin



Furosin

including jaundice, diabetes, and dropsy (Foo and Wong, 1992). It is used in the Ayurveda system of medicine to cure problems like the genitourinary system, kidney, liver, spleen, and stomach. The entire plant is used in menorrhagia and gonorrhea, and other genital affections. *P. amarus* is very useful in diarrhea, gastropathy, dysentery, ophthalmopathy, intermittent fevers, scabies, ulcers, and wounds (Jay Ram et al., 2011).

P. amarus has a long history in curing problems of kidney, liver, bladder, intestinal parasites, and diabetes. The Spanish name Chanca Piedra' means shatter stone or stone breaker. South American people, also called Chanca Piedra, used to reject kidney and gall bladder (Foo and Wong, 1992), and it is medicine for influenza (Foo, 1993a). Decoctions of *P. amarus* are used to treat uterus complaints, asthma, cramps, and labor (May, 1982; Titjari, 1985; Heyde, 1990; Sedoc, 1992; Nanden, 1998). *P. amarus* is used as a restoration herb and also as an appetizer, and as a tonic, also used as a colic. The plant is considered as diuretic when it is boiled along with leaves and used in treatment of diabetes, hepatitis, dysentery, ladies' menstrual disorders, and skin disorders (Wessels et al., 1976; Tirimana, 1987; Heyde, 1968, 1990). Whole plant extracts are used to treat malaria and anemia. *P. amarus* helps to release phlegm (Heyde, 1990) and also used as constipation (Tjong and Young, 1989).

58.3.1 ANTIDIABETIC AND HYPOGLYCEMIC ACTIVITIES

Alcoholic extract of *P. amarus* was found to have significant antidiabetic activity. Ethanol extract was found to reduce plasma cholesterol, triglycerides, low density lipoprotein cholesterol, VLDL cholesterol and atherogenic index, while there is a rise in high-density lipoprotein cholesterol) in diabetes mellitus (DM) animals (Bavarva and Narasimhacharya, 2007). Concordantly, seven days study carried out on noninsulin-dependent diabetic patients using water extract of aerial parts showed that it is not effective in lowering both fasting blood glucose and postprandial blood glucose level in untreated diabetic patients (Moshi et al., 2001). Relatedly, the ME of the plant has also been found to reduce blood sugar level in alloxan-induced diabetic rats (Raphael et al., 2002b).

The hypoglycemic potential of aqueous extract of whole plant was investigated in alloxan-induced diabetic Wistar albino rats. The extract showed at 260 mg/kg concentration a considerable reduction in blood glucose level by 112% at 24 h of oral administration. A reduction in blood glucose level of 81 and 61% (day 7) at doses of 130 and 260 mg/kg of extract were observed, respectively. The extract also showed a highly significant decrease in blood

glucose level of 38 and 30% (day 14). On the administration of 390 mg/kg dose of extract, a significant reduction in blood glucose level of 41% on day 7 and 16% on day 14 was observed (Mbagwu et al., 2011).

The anti-hyperglycemic and hypo-lipidemic activities were evaluated in streptozotocin (STZ)-induced diabetic male Wistar albino rats with aqueous extract of whole plant of *P. amarus* by Karuna et al. (2011). The extract was administered 200 mg/kg body weight/day to control rats and STZ-induced diabetic treated rats by gavage for 8 weeks. After the treatment period, plasma lipid profile of kidney LPO, protein oxidation and GSH were estimated. The considerable decrease in the body weight, hyperglycemia, and hyperlipidemia was observed in STZ-induced diabetic rats' group which treated with aqueous extract of *P. amarus*. STZ-induced diabetic rats revealed increased renal oxidative stress with increased LPO and protein oxidation (Karuna et al., 2011). The α-amylase inhibitory activity of ethanol, chloroform, and hexane extracts of *P. amarus* against porcine pancreatic amylase *in-vitro* was evaluated. The ethanol and hexane extracts showed considerable α-amylase inhibitory activity with an IC_{50} values 36.05 ± 4.01 and 48.92 ± 3.43 g/mL, respectively. However, the chloroform extract (CE) failed to inhibit α-amylase activity (Tamil et al., 2010). Hydro-alcoholic extract of leaves of *P. amarus* (HAEPA) was studied in rats for its *in-vivo* anti-hyperlipidemic potential by cholesterol diet induced hyperlipidemia model. Results indicated that HAEPA possessed significant hypo-lipidemic activity at 300 and 500 mg/kg concentration (Umbare et al., 2009).

58.3.2 DIURETIC AND ANTI-HYPERTENSIVE ACTIVITY

Nine mild hypertensives (4 of them suffering from DM) were treated with *P. amarus* whole plant for 10 days. Suitable parameters in the blood and urine samples were studied. Substantial increase was observed in 24 h urine volume, urine, and serum Na levels. A significant reduction was noted in systolic blood pressure in non-diabetic hypertensives. Blood glucose level was also reduced in the treated group. Clinical observations exposed no harmful side effects (Srividya and Periwal, 1995).

58.3.3 ANTI-DIARRHEAL, GASTROPROTECTIVE, AND ANTI-ULCER ACTIVITY

Pretreatment with *P. amarus* leaves water extract (500 mg/kg) and cimetidine (100 mg/kg) significantly inhibited ulceration by 59.3 (aqua.) and 41.2%

(cime.), respectively. The lower dosage of the aqueous extract had a higher ulcer inhibition and acetone extract had a dose-dependent percentage ulcer inhibition (Shokunbi and Odetola, 2008). Methanolic extract of aerial parts of *P. amarus* significantly inhibited gastric lesions on adult male Wistar rats, which induced by intra-gastric administration of absolute alcohol (8 mL/kg body weight). Mortality, increased ulcer index, stomach weight and intraluminal bleeding became lower significantly by *P. amarus*. *P. amarus* treatment significantly elevated the reduction of gastric mucosa GSH which induced by ethanol admission (Raphael and Khuttan, 2003). A gradient dose (100–800 mg/kg) experiment was conducted with water extraction to find out inhibition of gut meal travel distance in normal mice. The result showed the inhibition of 31.65% at 400 mg/kg concentration of *P. amarus* aqueous extraction as highest intestinal transit inhibition. Castor oil induced diarrhea in mice also worked at the same concentration (400 mg/kg) and delayed the diarrhea, reduced frequency of defecation gut meal travel distance significantly by 79.94% compared to 86.92% which produced by morphine (100 mg/kg) (Odetola and Akojenu, 2000).

58.3.4 ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY

Extract of *P. amarus* has an anti-inflammatory effect as well as prevent both ipsilateral and contralateral persistent nociception (Kassuya et al., 2003). Another study showed that *P. amarus* exhibited potent systemic antinociceptive actions (Santos et al., 1995). Water and MEs of *P. amarus* were found to have anti-inflammatory activity (Raphael and Kuttan, 2003).

58.3.5 HEPATOPROTECTIVE ACTIVITY

The protein isolate of *P. amarus* indicates hepatoprotective effect against acetaminophen-induced toxicity (Renuka and Rahim, 2017). Another study showed the effect of leaves water extract of *P. amarus* on matrix metalloproteinases. Administration of *P. amarus* extract significantly decreased the levels of collagen. *P. amarus* effectively modified alcohol and thermally oxidized polyunsaturated fatty acid-induced fibrosis (Surya Narayanan et al., 2011). The protective effect of phyllanthin, well known principal constituent on ethanol induced rat liver cell injury was evaluated. Phyllanthin confirmed its character in protection by antagonizing the ethanol effect on liver cells. Phyllanthin showed antioxidant activity of rat hepatocytes along with level of

total glutathione (GSH), and activities of SOD and GR, which were reduced by ethyl alcohol (Chirdchupunseree and Pramyothin, 2010).

It was also reported that a protein isolated from *P. amarus* protects against oxidative damage of hepatocytes induced by carbon tetrachloride (Bhattacharjee and Sil, 2007). The hepatoprotective activity of 50% ethanolic extract (EE) of aerial parts of *P. amarus* plant (every day for 30 days) against carbon tetrachloride (CCl_4)-induced liver damage in mice was determined. CCl_4 administration caused a major increase in liver and ALT, AST, ALP, and acid phosphatase (ACP), though total protein (TP) content pointedly decreased as related to vehicle control. It confirmed that the effect was dose dependent. Oral administration of water extract of *P. amarus* caused significant mitigation of CCl_4 induced changes (Krithika and Verma, 2009b). *P. amarus* attenuated the toxic effects of CCl_4 and caused a subsequent recovery towards normalization. Administration of *P. amarus* at 300 mg/kg body weight offered maximum recovery (98–100%) against CCl_4 (Krithika and Verma, 2009a).

58.3.6 NEPHROPROTECTIVE ACTIVITY

The aqueous extract of *P. amarus* 200 mg and 400 mg/kg/day dose for 14 days administrated, the results were found that the protection against the nephrotoxic effect in rat, it is by maintaining the level of blood urea nitrogen and serum creatinine at the normal range when compared to control group (Adeneye and Senebo, 2008). Another study resulted; the ethanol extract of the leaves of *P. amarus* was investigated for its nephroprotective activity against gentamicin induced nephrotoxicity in rats. Co-administration of the extract with gentamicin prevented kidney and improved all nephrotoxic parameters (physical, urinary, and blood) observed (Reddy et al., 2017). The extracts of *P. amarus* prepared by melting the leaves in olive oil for 7 and 14 days were tested for their ability to protect the kidney against cisplatin induced nephrotoxicity. The study revealed significant decrease in plasma concentrations of K^+, Cl-, creatinine, and urea in extract treated groups when compared to negative control value and significant increase in plasma concentrations of Na^+ and HCO^{3-} when compared to negative control value (Peters et al., 2015).

Single oral dose (100–400 mg/kg/day) of the leaves and seed water extracts (WEs) of *P. amarus* were investigated for their protective effects nephrotoxic Wistar rats for weeks. The acetaminophen nephrotoxic rats, 100–400 mg/kg/day significantly attenuated elevations in the serum creatinine and blood urea

nitrogen levels in dose related manner. Similar effects were recorded in the gentamicin experiment model of acute renal injury (Adeneye and Adokiye, 2008). Yao et al. (2018) reported the diuretic property of the ethanolic fraction of *P. amarus*.

58.3.7 HYPERLIPIDEMIC ACTIVITY

P. amarus has anti-hyperlipidemic effect. It was also reported that the aqueous extract exhibited anti-hyperlipidemic activity (Nwanjo et al., 2007). HAEPA also has anti-hyperlipidemic potential in hyperlipidemic rats (Khanna et al., 2002). Additionally, phyllanthin which is a bioactive compound of *P. amarus*, was administered for 12 weeks to mice co-fed with HFD (high fat diet); there was protection against HFD induced weight increase and adiposity, lowered the mRNA activity of adipogenic genes and highered the expression of lipolytic genes in white adipose tissue, lowered liver triglyceride accumulation, restoration of HFD induced serum lipid disturbances and reduced serum triglycerides and free fatty acids in HFD fed mice (Jagtap et al., 2016). The lipid-lowering activity of *P. amarus* was found to be controlled through inhibition of hepatic cholesterol biosynthesis, enhanced catabolism of LDL, and highering fecal bile acids excretion and activation of LCAT and tissue lipases (Umbare et al., 2009).

58.3.8 CARDIOVASCULAR (VASORELAXANT) EFFECT

It was reported that methyl brevifolincarboxylate (MB) isolated from the leaves of *P. amarus* exerted vasorelaxant effect on the aortic rings of rat (Iizuka et al., 2006). MB was also found to have a potent inhibitory effect against platelet aggregation (Iizuka et al., 2007). The aqueous extract of *P. amarus* was tested for its cardio-protective property against high-fructose (HF) diet induced cardiac damage (CD) in Wistar rats. The aqueous extract prevented the increase in levels of cardiac and aortic lipids and decreased phospholipids after co-administration with the HF for 60 days (Putakala et al., 2017).

58.3.9 APHRODISIAC ACTIVITY

Methanolic extract of *P. amarus* leaves caused a significant increase in the level of testosterone of the male guinea pigs, from 2.3 ± 0.06 to 3.9 ± 0.05 (7^{th} day) 4.3 ± 0.6 (14^{th} day) and 2.8 ± 0.6 (21^{st} day) after the administration

of the extracts. Furthermore, the methanolic extract of *P. amarus* (800 mg/kg) caused a decrease in the level of luteinizing hormone (LH) from 3.1 ± 0.22 to 3.0 ± 0.08 and follicle stimulating hormone (FSH) from 1.6 ± 0.50 to 1.5 ± 0.13 (Obianime and Uche, 2009).

58.3.10 CONTRACEPTIVE EFFECT

Antifertility effect of whole plant *P. amarus* alcoholic extract was investigated in cyclic adult female mice at a dose of 100 mg.kg body weight for 30 days orally. The results showed that there was no considerable change in absolute body weight and organ weight; it showed that there is no alteration in general metabolic status. Cohabited females with normal male mice were not able to become pregnant as their normal cyclicity was affected. These influences are related to a change in the hormonal milieu that directs female reproductive role. After withdrawal of feeding the plant extract for 45 days, these effects were reversible. So, alcoholic *P. amarus* extract shows a definite contraceptive activity in female mice (Rao and Alice, 2001).

58.3.11 SPASMOLYTIC ACTIVITY

Probable spasmolytic action of the extracts of *P. amarus* was judged by their ability to reduce forces of smooth muscle contraction of a 2 cm long piece of guinea pig ileum induced by EC_{50} acetylcholine (27±5 g/L) or EC_{50} histamine (102±13 g/L) (Mans et al., 2004).

58.3.12 IMMUNOMODULATORY ACTIVITY

The methanolic extract of *P. amarus* was examined for its respiratory burst effects. The effect of the extract of *P. amarus* on chemotactic migration of polymorphonuclear leukocytes was tested using the Boyden chamber technique (BCT). The extract of *P. amarus* formed the strongest oxidative burst of polymorphonuclear leukocytes with luminol-based chemiluminescence (Jantan et al., 2011). Around 75% methanolic extract of *P. amarus* at two doses 250 and 750 mg/kg body weight considerably reduced the myelosuppression and increased the WBC count, bone marrow cellularity as well as the number of maturing monocytes. *P. amarus* also increased the cellular GSH and GST, thus lessening the effect of toxic metabolites of CTX on the

cells. This plant did not decrease the tumor reducing activity of CTX. In fact, there was a combined action of CTX and *P. amarus* in dropping the solid tumors in mice (Kumar and Kuttan, 2005).

58.3.13 CANCER PROTECTION AND CYTOTOXICITY

P. amarus showed protection against chemical carcinogenesis. It was reported that the water extract considerably inhibited hepatocarcinogenesis in a dose-dependent manner on N-nitrosodiethylamine (NDEA) induced male Wistar rats (Jeena et al., 1999). Inhibition of cell cycle regulation, topoisomerase II, P450 enzymes as well as antioxidant activity may contribute to the overall activity of the extract against carcinogenesis (Rajeshkumar et al., 2002). *P. amarus* extract was found to considerably inhibit urinary mutagenicity created in rats by benzo-pyrene (Raphael et al., 2002a). The study showed that the ME of *P. amarus* has chemopreventive activity against MNNG-induced stomach cancer in rats (Raphael et al., 2006). The aqueous extract of *P. amarus* has also demonstrated anti-mutagenic and anti-genotoxic properties. In addition, the extract antagonizes DNA damage caused by DMN in hamster liver (Sripanidkulchai et al., 2002).

Cytotoxicity of the crude extracts and their two fractions of *P. amarus,* were screened using the MTS (3-(4,5-dimethylthiazol-2-yl)-5(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) reduction assay. It was shown to inhibit MCF-7 (breast carcinoma) and A549 (lung carcinoma) cells growth with IC_{50} values ranging from 56 to 126 gm/mL and 150–240 gm/mL for methanolic and aqueous extracts, respectively (Lee et al., 2011; Jay Ram et al., 2011).

58.3.14 TOXICITY STUDY

Toxicity study of aqueous extract of *P. amarus* showed that the extract can cause anemia because it is associated with decrease in the red blood cell/red blood corpuscles count, PCV, Hb concentration level of alanine aminotransferase (ALT); but there is a rise in the WBC count, levels of aspartate aminotransferase (AST), total conjugated bilirubin, TP and albumin (Adedapo et al., 2005a, b). Contrary to this Singh et al. (2016) reported that single oral dose and sub-acute toxicity study of *P. amarus* showed that the medicinal plant is non-toxic with an $LD_{50} > 5$ g/kg, which is a clear indication that it is safe, but associated with slight cytotoxic effect to the human adenocarcinoma cell

line (Singh et al., 2016). This may be as a result of variation in experimental conditions and procedure. However, Singh et al. (2016) reported an LD_{50} of 2590.984 mg/kg bw in Swiss albino mice model in laboratory condition when administered with aqueous extract of the plant. Doses above 2,500 mg/kg bw demonstrated a statistically signification elevation of urea level and histopathological changes were observed, with no significant increase in creatinine level (Guha et al., 2010). Another study showed that whole plant alcohol extract was not toxic as it displayed no effect on blood cell counts, Hb levels and serum biochemical parameters. Moreover, the body weights of test animals were not affected by the extract (Rao and Alice, 2001; Rao et al., 1997).

58.3.15 ANTIOXIDANT ACTIVITY

Karuna et al. (2011) reported antioxidant activity of aqueous extract of whole plant of *P. amarus* at the dose of 200 mg/kg body weight/day in STZ-induced diabetic male Wistar albino rats.

The water extract of *P. amarus* showed significant potential in scavenging free radicals, and in inhibiting lipid peroxidation (LPO). Also, the extract has a high content of phenolic compounds which are strong and significant positive correlations to free-radical scavenging activity (FRSA), cyto-protective efficiency and LPO inhibition capacity against Cr (VI)-induced oxidative cellular damage (Guha et al., 2010). FRSA of 50% EE of aerial parts of *P. amarus* extract and lignan phyllanthin was examined using DPPH assay. The FRSA was concentration-dependent in both cases. Phyllanthin exhibited very high antioxidative activity as compared to *P. amarus* extract (Krithika et al., 2009). The antioxidant action of some of its principal constituents, namely amariin, 1-galloyl-2,3-dehydrohexahydroxydiphenyl (DHHDP)-glucose, repandusinic acid, geraniin, corilagin, phyllanthusiin D, rutin, and quercetin 3-O-glucoside were inspected for their capacity to scavenge free radicals in a range of systems including DPPH, 2,2-azobis-3-ethylbenzthiazoline-6-sulfonic acid (ABTS)/ferrylmyoglobin, ferric reducing antioxidant power (FRAP) and pulse radiolysis. The compounds exhibited considerable antioxidant activities with divergent efficacy liable on the assays employed. Amariin, repandusinic acid and phyllanthusiin D exhibited higher antioxidant activity among the ellagitannins and were comparable to the flavonoids, rutin, and quercetin 3-Oglucoside (Londhe et al., 2008). Pretreatment with *P. amarus* leaf extract on antioxidant enzymes in gastric mucosa homogenate

was studied. Significant reductions in the gastric mucosa CAT, SOD, and GST activities were observed in the ethanol group compared with the normal control group. *P. amarus* acetone extracts (1,000 mg/kg) and cimetidine (100 mg/kg) caused an elevation by 53 and 52% for CAT, 8 and 14% for SOD, and 33 and 38% for GST, respectively when compared with the ethanol group. Acetone extract produced a dose-dependent increase whereas 500 mg/kg of the aqueous extract seems more effective (Shokunbi and Odetola, 2008). Methanolic extract of leaves and stems of *P. amarus* was found to have potential antioxidant activity *in-vitro* (Raphael et al., 2002b). Amariin, repandusinic acid, phyllanthusiin D, phyllanthin, and phenolic compounds isolated from *P. amarus* showed remarkable antioxidant activity (Jay Ram et al., 2011). *P. amarus* alleviated oxidative stress induced by nimesulide in the liver as evident by rapidly restoring most of the Nimesulide-induced oxidative changes related to those obtained by the self-recovery of liver (Sarkar et al., 2005).

58.3.16 ANTI-PLASMODIAL ACTIVITY

Whole plant extracts (both water and ethanolic) of *P. amarus*, in different doses to Swiss albino mice showed prophylactic and chemotherapeutic properties against *Plasmodium yoelii* infection (Jay Ram et al., 2011). The water extract showed a little higher effect than the EE. The anti-plasmodial effects of extracts (water and ethanolic) were comparable to the typical prophylactic and chemotherapeutic drugs used in chloroquine resistant plasmodium infection. The extracts showed prophylactic effect by significant delay in the onset of infection with the suppression of 79% at a dose of 1,600 mg/kg/day. The results show that the extracts of the whole plant possess source and chemotherapeutic effects against strong strains of *P. yoelii* in Swiss albino mice (Ajala et al., 2011). Mice treated with 12.5, 25, 50, 100, 150, 200, 250 mg/kg body weight for 3 days, orally showed a considerable result against *P. berghei* and *P. falciparum* parasites grown *in vivo* (Traore et al., 2008). The water extract of aerial parts showed a significant dose-dependent suppression of *P. berghei* parasites (Dapper et al., 2007). Ethanolic, methanolic, and methylene chloride extracts of entire plant of *P. amarus* showed significant activity against the chloroquine sensitive strain of *P. falciparum* 3D7. The IC_{50} of methylene chloride extract and methanolic extract was 14.53 and 5 g/mL, respectively (Adjobimey et al., 2004).

58.3.17 ANTI-NEMATODAL ACTIVITY

Two compounds isolated from *P. amarus*, 8-(3-methyl-but-2enyl)-2-phenyl chroman-4-one and 2-(4-hydroxyphenyl)-8-(3-methyl-but-2enyl)-chroman-4-one were found to have anti-nematodal activity against *Meloidegyne incognita* and *Rotelenchulus reniformis* (Shakil et al., 2008).

58.3.18 ANTI-FUNGAL ACTIVITY

Inhibition zones were observed in different polar and low polar solvent extracts of aerial parts. It was resolved that *P. amarus* aerial part CE showed considerable inhibitory effect on dermatophytic fungi *M. gypseum* (Agrawal et al., 2004).

58.3.19 ANTI-BACTERIAL ACTIVITY

P. amarus has broad spectrum antibacterial activity on both gram-positive and gram-negative bacteria. A study carried out on various bacterial strains like *Bacillus subtilis, B. stearothermophilus, Staphylococcus aureus, Micrococcus leuteus, Proteus mirabilis, P. vulgaris, Salmonella typhi* and *Enterobacter aerogens* revealed that *P. amarus* showed the least MIC on all bacteria tested (Komuraiah et al., 2009). Similarly, the methanolic extract of *P. amarus* was found to have potent inhibitory effect against drug-resistant pathogenic gram-negative bacteria; *Shigella* spp., *E. coli, V. cholerae, S. aureus, S. typhimurium, P. aeruginosa, B. subtilis, Klebsiella,* and *Streptococcus* sp. in a dose-dependent manner (Mazumder et al., 2006).

Hexane, methanol, and aqueous extracts of aerial parts of *P. amarus* were tested against *Bacillus subtilis, Salmonella typhi, Escherichia coli, Candida albicans, Pseudomonas aeruginosa* and *Staphylococcus aureus* using the agarcup diffusion protocol (Jay Ram et al., 2011). The aqueous and methanolic extracts were more active against all the bacteria microorganisms. Methanolic extract also showed many activities with a minimum concentration that is 1.56 mg/mL against all the test microorganisms (Alli et al., 2011). Eldeen et al. (2011) reported antibacterial activity of *P. amarus* against *S. aureus* (gram-positive) here MIC value of 17.7 g/mL. The antibacterial activity of EEs of the root and leaf of *P. amarus* was tested against *E. coli* which was isolated from the stool samples of HIV positive patients. The strains isolated from both HIV +ve patients were vulnerable to various doses of the plant

extracts (5, 10, 20, 40, and 80 mg/mL). The MIC and MBC of the plant extracts ranging from 520 to 530 mg/mL, respectively (Akinjogunla et al., 2010). *P. amarus* exhibited remarkable bioactivity against ocular infections causing bacteria *P. aeruginosa, Micrococcus lylae, Staphylococcus hominis, S. aureus, S. haemolyticus, Micrococcus luteus, Bacillus lentus, B. firmus* and *Pseudomonas stutzeri* (Koday et al., 2009). Antimicrobial properties aqueous and methanolic extracts of leaves of *P. amarus* at the concentration of 100 mg/mL were tested against *E. coli, Streptococcus* spp., *Klebsiella* spp., *Pseudomonas* spp. and *Staphylococcus* spp. Methanolic extract of the plant was more effective (611 mm) than WEs (510 mm) inhibiting the growth of pathogenic bacteria but was less potent when compared to that of ofloxacin (19 mm) and ciprofloxacin (21 mm) used as positive controls (Okoli et al., 2009). Around 80% methanolic extract of whole plant of *P. amarus* showed the least MIC on the tested bacteria viz. *B. stearothermophilus, S. aureus, B. subtilis, M. leuteus, S. typhi, Enterobacter aerogens, Proteus mirabilis*, and *P. vulgaris* with 30 and 40 g/mL MIC and MBC, respectively (Komuraiah et al., 2009) for this work.

The essential oil and its fractions obtained from fresh leaves and seeds of *P. amarus* were tested on *B. subtilis*, *Citrobacter* sp., *E. coli*, *E. faecalis*, *K. pneumoniae*, *P. aeruginosa*, *P. mirabilis*, *S. aureus, S. albus* (isolate) and *C. albicans*. All the test samples of essential oil and fractions tested activity (11–20 mm diameter zone of inhibition) against the microorganisms except *P. aeruginosa* (Ogunlesi et al., 2009).

58.3.20 ANTIVIRAL ACTIVITY

Inhibitory effect of root and leaves methanolic extracts of *P. amarus* on the enzymes of hepatitis-C virus were screened *in-vitro*. Effect was investigated on viral RNA replication. *P. amarus* root extract showed significant inhibition of HCV-NS3 protease enzyme; however, *P. amarus* leaves extract showed great inhibition of NS5B in the *in-vitro* assays (Jay Ram et al., 2011). Both *P. amarus* root and leaves extracts did not show any cytotoxicity (Ravikumar et al., 2011). *P. amarus* root extract inhibited HCV-RNA replication. Results suggested that the possible inhibitory activity of *P. amarus* extract against HCV would help for optimizing specific antiviral agent (Ravikumar et al., 2011).

An aqueous extract of *P. niruri* (*P. amarus*) inhibits endogenous DNA polymerase of hepatitis B and binds to the surface antigen of hepatitis B

virus *in-vitro* (Venkateswaran et al., 1987). Also, *in-vivo* study shows that the extract of *P. amarus* has effect against Hepatitis B virus in infected human (Blumberg et al., 1990). Another study revealed that the extract blocked enzymes that play a vital role in the reproduction of hepatitis B virus (Naik and Juvekar, 2003). Oral administration of *P. amarus* was found to decrease the mortality rate and considerably increase the survival of hepatocellular carcinoma harboring animals (Rajeshkumar and Kuttan, 2000). The therapeutic activity of plant extracts of *P. amarus* and *P. maderaspatensis* for post exposure prophylaxis against infection by Hepadnaviruses was tested in ducklings infected by the DHBV (Munshi et al., 1993). *P. amarus* polyphenols contents are representatives of simple phenols flavan-3-ols (epigallocatechin 3-gallate), (shikimic acid 3-and 5-O-gallate), and hydrolyzable tannins (casuariin, corilagin, geraniin) and proanthocyanidins (a hexamer) were used for *in vitro* studies for gene expressions (iNOS, IL-18, IL-12, IL-11, IL-11, TNF-, IFN-, and by RT-PCR) (Kolodziej et al., 2005).

P. amarus derivatives of extracts blocked the interaction of HIV-1 gp120 with its primary cellular receptor CD4 at 50% concentration of 2.65 (water-alcohol extract) to 0.48 μg/mL (geraniin). Inhibition was a proof for the HIV-1 enzymes integrase (0.48–0.16 μg/mL), reverse transcriptase (RT) (8.17–2.53 μg/mL) and protease (21.80–6.28 μg/mL) (Notka et al., 2004). Aqueous as well as alcohol-based *P. amarus* extracts potently inhibited HIV-1 replication in HeLa CD4+ cells with 50% effective concentration (EC_{50}) values ranging from 0.9 to 7.6 μg/mL.

A gallotannin augmented fraction showed improved activity (0.4 μg/mL), and the purified gallotannins geraniin and corilagin were most active (0.24 μg/mL). HIV-1 replication was also blocked in $CD4^+$ lymphoid cells with comparable EC_{50} values. Applying cell-based internalization assay, it was demonstrated 70–75% inhibition of virus uptake at concentrations of 2.5 μg/mL for the water alcohol extract and geraniin. In addition, a concentration dependent inhibition of HIV-1 RT was demonstrated *in vitro*. The 50% inhibitory concentration (IC_{50}) values varied from 1.8 to 14.6 μg/mL (Notka et al., 2003).

58.3.21 EFFECT ON REPRODUCTIVE ORGANS

The effect of recovering from the damaged estrous cycle with treatment of *P. amarus* lignans viz. phyllanthin and hypophyllanthin was studied by Adedapo et al. (2003). Hypophyllanthin and phyllanthin at the dose of 100 mg/kg body

weight have been found to be significantly transformed into enterolignan(s), which is known to be responsible for augmenting estrous cycle in rats (Islam et al., 2008). *P. amarus* aqueous crude extracts were administered to sexually mature male albino rats to determine the potentiality of extract on the male reproductive organs. The aqueous crude extracts of *P. amarus* caused a reduction in the mean seminiferous tubular diameter (STD) and varying degrees of testicular degeneration in the tested rats (Adedapo et al., 2003).

58.3.22 RADIOPROTECTIVE EFFECT

P. amarus was studied for radioprotective effect by using rat pBR322 plasmid DNA and liver mitochondria as an *in vitro* model system. Repandusinic acid, geraniin, Ellagitannins (amariin, 1-galloyl-2, 3-dehydrohexahydroxydiphenyl (DHHDP)-glucose, phyllanthusiin D, corilagin,) and flavonoids (quercetin 3-O-glucoside and rutin) at the concentration of 0.4, 0.3, 0.2, and 0.1 nM significantly prevented protein oxidation and LPO in mitochondria. The chemical constituents also prevented radiation induced single strand breaks in pBR322 plasmid DNA (Londhe et al., 2009). Around 75% methanolic extract of *P. amarus* aerial parts at concentrations of 750 and 250 mg/kg body weight on BALB/c mice were used in intestine to elevate the antioxidant enzymes in the and decrease the LPO levels. Histopathological evaluations revealed that decreased damage to intestinal cells. *P. amarus* was found to protect the clastogenic effects of radiation. It showed a decreased number of micronuclei. The administration of *P. amarus* was also reported to decrease percentage of the chromosomal aberrations (Harikumar and Kuttan, 2007). Kumar and Kuttan (2004) investigated the radioprotective effect of 75% methanolic extract of aerial parts of *P. amarus* in adult BALB/c mice. *P. amarus* extract significantly increased the bone marrow cellularity, total WBC count and α-esterase activity. *P. amarus* also increased the activity of GR, SOD, CAT, GST, and GPX, both in tissue and blood which were reduced by radiation treatment. They showed a significant increase in GSH levels of tissue and blood also observed. LPO levels, increased after radiation, were potentially reduced by *P. amarus* treatment, both in liver and serum (Kumar and Kuttan, 2004).

58.3.23 ANTI-AMNESIC ACTIVITY

The effect of water extract of aerial parts of *P. amarus* was evaluated for brain cholinesterase and cognitive functions activity in mice. *P. amarus* (200,

100, and 50 mg/kg) observed improvement in memory scores of older and young mice. *P. amarus* also reversed significantly the amnesia induced by diazepam (1 mg/kg, i.p.) and scopolamine (0.4 mg/kg, i.p.) potentially brain cholinesterase activity was also reduced (Joshi and Parle, 2007). Nootropic activity of [6]-gingerol and phyllanthin was studied in mice. Phyllanthin (7.5 and 15 mg/kg, p.o.) and [6]-gingerol (25 and 50 mg/kg, p.o.) [6]-gingerol and phyllanthin increased step-down latencies significantly in the aged mice, scopolamine, and diazepam induced amnesic mice as compared with piracetam (200 mg/kg, i.p.). [6]-gingerol and phyllanthin decreased acetyl-cholinesterase activity (Joshi and Parle, 2006).

KEYWORDS

- ***Phyllanthus amarus***
- **hepatitis virus**
- **diabetes mellitus**
- **nephroprotective activity**
- **phyllanthin**
- **streptozotocin**

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CHAPTER 59

Bioactives and Pharmaco-Constituents of a Unani Drug – *Phyllanthus maderaspatensis* L.

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59.1 INTRODUCTION

Unani is one of the traditional systems of alternative medicine originated in ancient Greece and it is now widely practiced in the Indian subcontinent. *Phyllanthus maderaspatensis*, is a popular Unani drug, belongs to the family Phyllanthaceae, has gained its specific epithet "*maderaspatensis"* referring to the place of its origin, the "Madras City of India" (currently known as Chennai, Tamil Nadu State). The species is widely distributed in tropical parts of India, Myanmar, Sri Lanka, Tropical Africa, Java, China, and Australia (Anju and Idris, 2019).

P. maderaspatensis is commonly known as Madras leaf flower (English), *Nilla-nelli* (Tamil), *Hajarmani* (Hindi), *Bhuiavali* (Marathi), *Nallausirika* (Telugu), *Madaraasnelli* (Kannada), *Kanocha* (Konkani), and *Thumyaa-malaki* (Sanskrit) (Leelaprakash and Dass, 2011). It is herbaceous plant with

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woody stem and 0.15–0.9 meters tall. The plant is monoecious with spiral leaves and oval stipules. The leaves are leathery, grayish green, and has round base. Apex is short and acuminate. The inflorescence is axillary fascicles. Fruit is a capsule, oblate, olive green in color with a smooth texture. The seed is three-sided, light brown color. The seed has unique rows of minute tubercles on them.

P. maderaspatensis has mucilaginous properties and also has been considered as an effective hepatoprotective agent. They are considered astringent, bitter, stomachic, diuretic, febrifuge, and antiseptic. They can also cure headaches, bronchitis, earache, and ophthalmic. The powder obtained from the dried plant material can be mixed with milk and consumed to treat jaundice (Rani et al., 2014).

59.2 BIOACTIVE COMPOUNDS

Root and shoot extracts of *P. maderaspatensis* are rich in secondary metabolites such as alkaloids, anthocyanins, anthracene, glycosides, coumarins, flavonoids, flavones, flavonols, phenols, dichlorochalcone, catacholic compounds, iridoids, gums, mucilages, carbohydrates, and steroids (Swarupa et al., 2014). Phytochemical screening revealed that, *P. maderaspatensis* consists of huge amounts of tannins, lignins, followed by ellagic acid, phenols, trace amount of iridoids and triterpenoids. Fibrous mucilage obtained from the seed cake can be hydrolyzed to galactose, rhamnose, and aldobionic acid. The active principal is the Gallic acid, Ellagic acid and Tannins (Komuraiah et al., 2009).

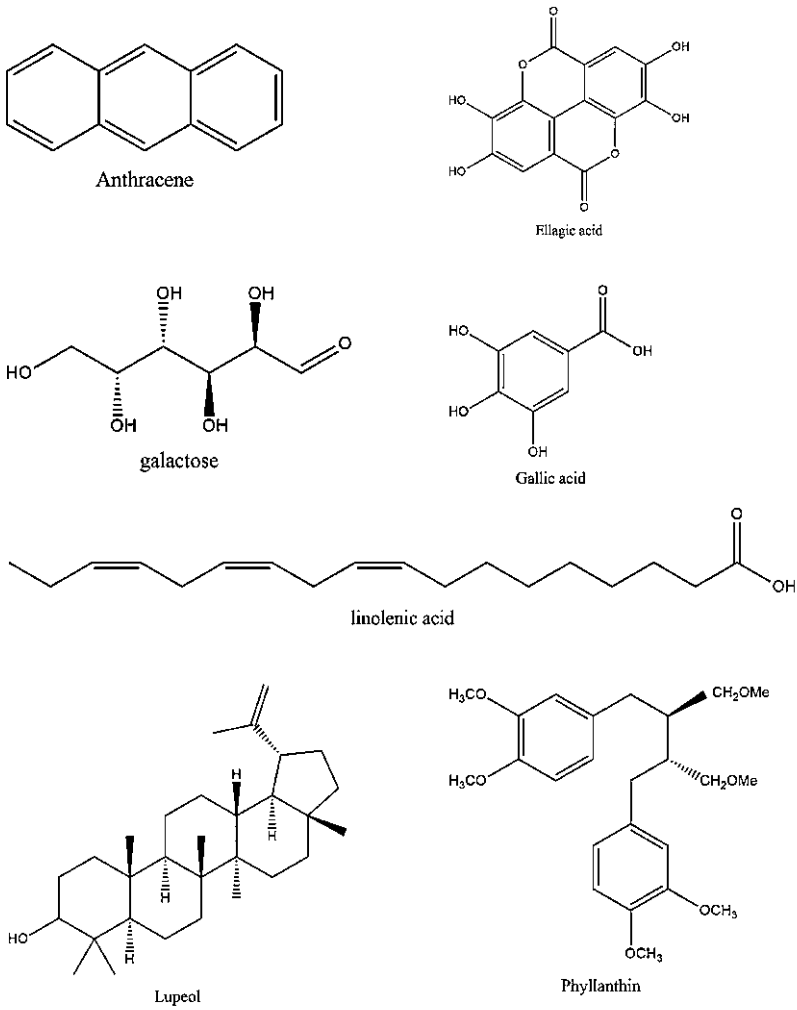
The HPTLC fingerprints of the plant *P. maderaspatensis* was shown the presence of Lupeol in the hexane extract. Phyllanthin is the major bioactive compound reported in the ME of *P. maderaspatensis* (Ravinchandran et al., 2012). The dried seed oil has myristic, palmitic, stearic acid, oleic, and linolenic acids. Maderin, a reddish brown coloring matter and an essential oil had also been reported (Khare, 2004).

59.3 PHARMACOLOGY

59.3.1 HEPATOPROTECTIVE ACTIVITY

The alcoholic and the aqueous extract of *P. maderaspatensis* was reported to possess hepatoprotective activity (Srirama et al., 2012). This significant hepatoprotective property may be due to the presence of high content of triterpene, tannins, and flavonoids (Rajasekar et al., 2014).

Chemical compounds found in *Phyllanthus maderaspatensis* L.



59.3.2 ANTI-BACTERIAL ACTIVITY

The aqueous extract of the species *P. maderaspatensis* showed resistance against bacteria such as *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebseilla pneumoniae* and *Salmonella typhimurium*. This indicates the anti-microbial activity of the species (Leelaprakash and Dass, 2011).

59.3.3 ANTI-FIBROTIC STUDY

The hexane extract of *P. maderaspatensis* inhibited the proliferation of activated LX-2 cell and suppressed the fibrotic gene expression along with functional restoration. This indicates the anti-fibrotic property of the species (Krishnakumar et al., 2016).

59.3.4 ANTI-CANCEROUS ACTIVITY

The *in vitro* cytotoxic studies of *P. maderaspatensis* showed 96.03% of cell death at 1,000 µg/ml. The study also reported that the cytotoxic effect was dose-dependent (Ravichandran et al., 2012). Silver nanoparticles synthesized from *P. maderaspatensis* inhibited cell proliferation of MCF 7 cells with an IC_{50} value of 67.23 µg/mL of the concentration (Kokila et al., 2016).

59.3.5 ANTI-CATALEPTIC ACTIVITY

The aqueous extract of leaves of *P. maderaspatensis* inhibited clonidine induced catalepsy and stabilizes mast cells. Thus, the polar constituents of the plant *P. maderaspatensis* are used as anti-histaminic and in the treatment of asthma (Nirmal et al., 2009).

59.3.6 CHEMOPROTECTIVE PROPERTY

The ethanol extract of *P. maderaspatensis* showed chemoprotective property on Adriamycin (ADP) induced toxicity and oxidative stress in mice (Bommu et al., 2007). The plant also exhibited chemoprotective effect in modulating and genotoxicity in Swiss albino (Chandrasekar et al., 2006).

59.3.7 ANTI-BACTERIAL ACTIVITY

The aqueous, alcoholic, and hydroalcoholic extracts of the seeds of *P. maderaspatensis* showed resistance against gram-positive *B. cereus, C. xerosis, S. pyogenes, S. epidermidis, S. aureus* and *S. mutans* and gram-negative *P. vulgaris, P. aeruginosa, K. pneumoniae* and *E. coli* bacterial at three different concentrations of 5 µgm, 10 µgm and 20 µgm. Inhibitory effects were more at the intermediate concentration, i.e., at 10 µgm/µL (Akhtar et al., 2020).

59.3.8 ANTI-INFLAMMATORY ACTIVITY

The hydro-alcoholic extract of on *P. maderaspatensis* repeated column chromatography of yielded Corilagin, an ellagitannin (β-1-*O*-galloyl-3,

6-(*R*)-hexahydroxydiphenoyl-d-glucose) compound, reported to be responsible for anti-inflammatory activities (Kochumadhavan et al., 2019).

59.3.9 ANTI-HYPERCHOLESTEROMIC ACTIVITY

Methanolic extracts of *P. maderaspatensis* reduced total cholesterol (TC) and triglycerides after 14 days of consumption in rats. This shows the anti-hypercholesteromic activity of *P. maderaspatensis* (Dissanayaka et al., 2019) (Table 59.1).

TABLE 59.1 Details of the Chemical Compounds Found in *Phyllanthus maderaspatensis* L. and its Pharmaceutical Properties

Sl. No.	Bioactive Compounds	Properties	References
1.	Flavonoids	Hepatoprotection	Rajasekar et al. (2014)
2.	Triterpenes	Hepatoprotection	Rajasekar et al. (2014)
3.	Tannins	Hepatoprotection	Rajasekar et al. (2014)
4.	Saponins	Anti-hypercholesteromic	Dissanayaka et al. (2019)
5.	Terpenoids	Anti-hypercholesteromic	Dissanayaka et al. (2019)
6.	Steroids	Anti-hypercholesteromic; hepatoprotection	Dissanayaka et al. (2019); Rajasekar et al. (2014)
7.	Phenols	Anti-hypercholesteromic; antioxidants	Dissanayaka et al. (2019); Upadhyay et al. (2014)
8.	Alkaloids	Anti-hypercholesteromic	Dissanayaka et al. (2019)
9.	Glycosides	Anti-hypercholesteromic	Dissanayaka et al. (2019)
10.	Gums	Anti-hypercholesteromic	Dissanayaka et al. (2019)
11.	Mucilages	Anti-hypercholesteromic	Dissanayaka et al. (2019)
12.	Carbohydrates	Anti-hypercholesteromic	Dissanayaka et al. (2019)
13.	Gallic acid	Hepatoprotective; chemoprotective	Sharma et al. (2011); Krishnaveni and Mirunalini (2012)
14.	Phyllanthin	Hepatoprotective; anti-cancer; anti-diabetic; immunosuppressant; anti-microbial; anti-inflammatory	Srirama et al. (2012); Azam and Ajitha (2017)
15.	Iridoids Corilagin	Anti-inflammatory; anti-inflammatory	Smithson et al. (2017); Kochumadhavan et al. (2019)
16.	Anthocyanins	Antioxidants	Upadhyay et al. (2014)
17.	Ellagic acid	Chemoprotective	Krishnaveni et al. (2012)
18.	Coumarins	Asthma treatment and lymohedema	Farinola and Piller (2005)
19.	Lupeol	Anti-inflammatory; anti-tumor; anti-arthritis; anti-malarial; chemoprotective; hepatoprotective	Gallo and Sarachine (2009)

KEYWORDS

- **anti-bacterial activity**
- **anti-cancerous activity**
- **chemoprotective property**
- **hepatoprotective activity**
- ***Phyllanthus maderaspatensis***

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CHAPTER 60

Pharmacological and Bioactive Principles of Bristly Starbur (*Acanthospermum hispidum* DC.)

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60.1 INTRODUCTION

Acanthospermum hispidum is commonly known as goat's head, starbur, hispid starbur, bristly starbur and belongs to the family of Asteraceae. It is an annual plant, branched, to 60 cm in height. Obovate, elliptic leaves of 1.5 cm–7 cm length are with serrated margins. Flowers are in head inflorescence. Around 5–9 ray flowers are present in single head with yellow petals. It has achene fruit. Triangular and flattened type of fruits are 5–10 cm long; fruits have a bristly appearance. *Acanthospermum hispidum* is native to Northern South America. It has been introduced to Africa and India from South America. In Brazil, it was identified as a weed in cotton-growing areas that has pharmacological properties (Chakraborty et al., 2012). It was found to be an invasive weed species in most of the agricultural farmlands. The root is 20 cm long with more number of secondary roots, which produces a pleasing aroma. Leaves give a bitter taste. Fine hairs are there on stems. It is used as a raw material to produce syrup which cures asthma. In traditional medicine, leaves are used in therapeutic infectious diseases (Summerfield et al., 1997). It possesses many ethnobotanical uses. It is also used in treating malaria, vomiting, headache, abdominal pain, stomachache, epilepsy, eruptive fever, constipation, blennorrhea, jaundice, bronchitis, cough, and skin disorders.

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It also possesses pharmacological properties like antidiabetic, carminative, anti-fungal, anti-helminthic, anti-hypertensive, and so on (Roy et al., 2010). In Burkina Faso, it is one of the traditional medicines that can treat many diseases (N'do et al., 2018).

60.2 BIOACTIVES

Acanthospermum hispidum has been found to possess more active chemical compounds. Studies show that the plant has compounds like n-hepatacosanol tricontane, n-butyl eicosanate; aerial parts have sesquiterpene lactones, glycosides, carbohydrates, glucuronic acid, loliopide, melampolide, mannitols; roots have caffeic acid esters, tridecapentayane, β-caryophyllene, bicyclogermacrene, α-bisabolol, α-humulene, carvacrol, methyl carvacrol (Araújo et al., 2008). It has been used for treating inflammations, anti-plasmodial, anti-protozoal effects like trypanocide (Adepiti et al., 2014). *A. hispidum* has many phytochemicals, sesquiterpene lactones, polyphenols, volatile oils, salvigenin, and nevadensin. The bioactive compounds are responsible for the medicinal properties possessed by the plant. Leaves of the plant can cure gonorrhea, dysentery, and hematuria. Entire plant parts attribute to treat various types of fever, bronchitis, contraceptive, cough, and abortive. Roots are responsible for curing allergic bronchitis, cough dysentery (Araújo et al., 2008). It also benefits curing memory problems and possesses anticholinesterase properties (Elufioye et al., 2016). The sweetness of the plant is because of its sugars and polyols. Acanthospermal B, acanthospermal B epoxide, hispidunolide A, and B are the sesquiterpene lactones present in the plant. Flavones like 5′-acetoxy 5,7,2′-trihydroxy-3,4′ dimethoxyflavone and 5,7,2′,5′,-tetrahydroxy-3,4′-dimethoxy flavone are separated from the leaves of the plant. The plant also contains N-butil eicosanate, N-heptasonol tricontane (Chakraborty et al., 2012). Usually, medicinal plants have good cholinesterase inhibiting compounds. *A. hispidum* is also proved to have rich cholinesterase inhibitors, which plays a vital role in memory regain. These sesquiterpene lactones in the Asteraceae family play a considerable role. Studies proved that about 900 of all chemical compounds showed pharmacological properties (Araújo et al., 2008). Essential oil of the *Acanthospermum hispidum* has α-humulene, β-caryophyllene, germacrene D, bicyclogermacrene, carvacrol, methyl carvacrol, α-bisabolol and nonanal (Alva et al., 2012). Few important bioactive compounds in *Acanthospermum hispidum* are given in Figure 60.1.

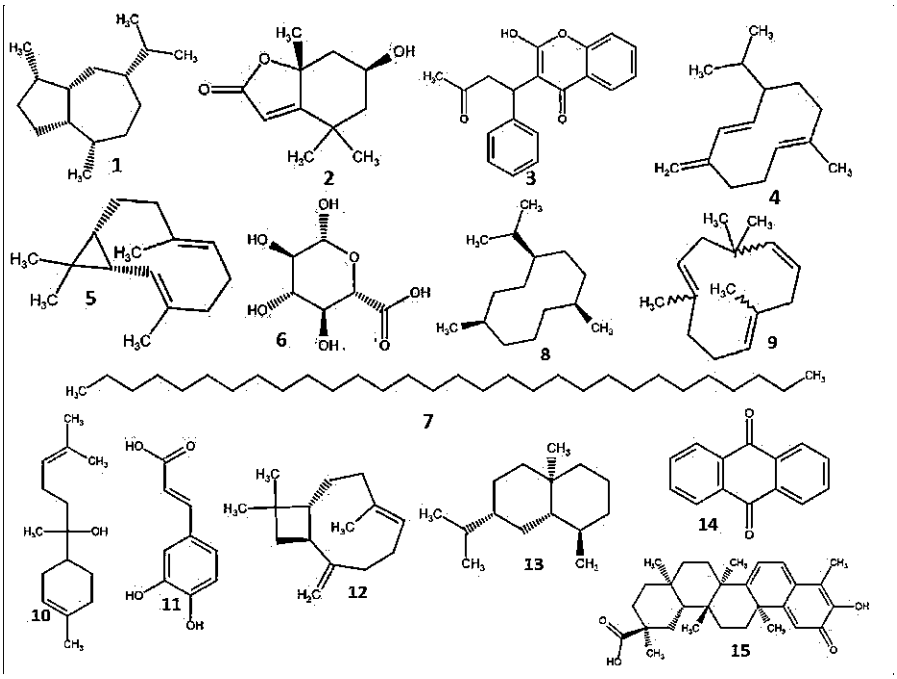


FIGURE 60.1 The chemical structures for the bioactive compounds in *Acanthospermum hispidum*. Guanine (1); loliolide (2); coumarins (3); germacrene D (4); bicyclogermacrene (5); glucuronic acid (6); triacontane (7); germacrane (8); α-humullene (9); α-bisabolol (10); caffeic acid (11); β-caryophyllene (12); eudesmane (13); anthraquinone (14); and triterpene (15).

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

60.3 PHARMACOLOGY

60.3.1 ANTIOXIDANT AND HEPATOPROTECTIVE ACTIVITY

Free radical scavengers are also called antioxidants because they prevent the damage of cells caused by free radicals. Nowadays, there has been a vast interest in searching natural antioxidants because it helps cure infectious diseases like cardiovascular, eye problems, diabetes, and cancer. A wide range of compounds like nitrogen, phenolic, and carotenoids are present in natural oxidants. *Acanthospermum hispidum* has antioxidant properties. Various methods to determine ROS scavenging activity against hydrogen peroxide, reducing power assay, nitric acid scavenging assay and phospho-molybdenum methods are used to trace the antioxidants levels in *Acanthospermum*

hispidum. Results indicate that ethanolic extract (EE) of the plant proved to possess significant antioxidant actions by all the above methods. It also proved that plants with rich portions of phenolic compounds have a substantial effect against reducing power, hydrogen peroxide, hydroxyl radical mitigation and nitric oxide (NO) scavenging. These compounds present in the plant helps to inhibit carcinogenesis and mutagenesis in human beings. These are mainly because of the hydroxyl group in a plant that is naturally available (Gomathi et al., 2013).

The antioxidant and hepatoprotective action of *Acanthospermum hispidum* were experimented with Wistar rats. Hepatotoxicity is induced by Carbon tetrachloride. Administration of hydroethanolic extract of the plant orally at a dose of 250 and 500 mg per kg resulted in reduced levels of alkaline phosphatase (ALP), amino transaminase (ALT) and aspartase amino transaminase (AST), leading to an excellent hepatoprotective effect. It also states that hydroethanolic extract of the plant helps cure liver diseases caused by carbon tetrachloride induction in rats, mediated through antioxidant activities (Kpemissi et al., 2015). Another test was conducted to identify the above activities within six groups of rats. *In vivo* test shows that EE of the plant has suitable antioxidant activities by testing in 2,2′-azinobis (3-ethylbenzolin-6-sulfonate) (ABTS) test and 2,2-diphenyl-1-picrylhydrazl (DPPH) test. *In vivo* test shows that EE of the plant with rich phenolic compounds possess good hepatoprotective capacity, proving that it can be used as traditional medicine in Burkina Faso to cure liver disorders (N'do et al., 2018).

60.3.2 ANTI-BACTERIAL AND ANTI-FUNGAL ACTIVITIES

In a study, *Acanthospermum hispidum* plant extract was prepared by removing the fruits and Whatman filter paper no. 41 is used for filtration. Bacterial cultures were inoculated in MH agar for the antibacterial test. Sabouraud dextrose agar (SDA) medium is used as a medium for studying antifungal activity. The antifungal results are compared with standard clotrimazole, proving that 50% aqueous extract of *A. hispidum* arrested *Penicillium chrysogenum, Microsporum gypseum, Aspergillus niger* and *Epidermophyton floccosum* in higher concentrations of the extract. In the lower concentrations, these extracts were found to be ineffective in comparison with the microbes tested. The *Acanthospermum* family possesses a group of chemical compounds called diterpenes responsible for all the antibacterial and antifungal properties. Other than diterpenes, the existence of monoterpenoids,

sesquiterpene lactones, triterpenoids, alkaloids, flavones, amino acids and saponins are present in this extract (Deepa et al., 2007).

Copper oxide nanoparticles are obtained from the leaf extract of *A. hispidum;* it was tested against two gram-positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*) and a gram-negative bacterium, *Escherichia coli*. Muller Hinton agar well method is preferred for testing these extracts. The extracted copper oxide nanoparticles proved to possess a high inhibition zone because they have more penetration and contact for micro-organisms. By this way it gives space for amines and carboxyl groups in the cell surface. Results proved that copper oxide nanoparticles extracted from *Acanthospermum hispidum* had provided the inhibition zone of 10 mm, 20 mm, and 13 mm for *Bacillus cereus, E. coli* and *Staphylococcus aureus*. The study concluded that *A. hispidum* has higher inhibition for gram-negative bacteria. The extracts have reliable antibacterial effects against gram-positive and gram-negative bacteria (Gowri et al., 2019).

Another study was conducted to screen phytochemical and antimicrobial activities of aerial parts of the *Acanthospermum hispidum*. From the aerial parts, acetone, petroleum ether, and ethanol extracts were prepared. Agar well diffusion method was used for this study. *Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Clostridium botulinum, Salmonella typhi, Listeria monocytogenes* and *Proteus mirobilis* were the eight strains taken for the test. Results of phytochemicals screening concluded that cardiac glycoside, carbohydrate, saponins, anthraquinone, alkaloids, triterpene, flavonoids, steroids, and tannins were present. The acetone extract has an inhibiting zone of 21–31 mm. However, *Bacillus subtilis* was not inhibited by any of these extracts. While compared to other extracts, acetone extract was very active, proving it has antimicrobial properties and might be used to prevent the infectious disease produced by the pathogen (Okoro et al., 2017). To study the anti-viral activity, aqueous extracts of the leaves of the *A. hispidum* are obtained. *A. hispidum* aqueous extract shows anti-viral activities against retroviruses and herpesvirus (Summerfield et al., 1997).

60.3.3 ANTI-MALARIAL ACTIVITY

Pharmacological tests were done to check whether the plant has antiplasmodial properties or not. Extracts were are prepared from the plant by drying the leaves and make them into a powdered form. These plants were tested

in the *in-vitro* condition against two clones related to *Plasmodium falciparum*. The clones are D6 chloroquine-sensitive strains and W2 chloroquine resistant strains. The results indicated that extract obtained from the plant is 200-fold more efficient than the standard. *Acanthospermum hispidum* showed a significant inhibitory effect (Sanon et al., 2003). Another study was done *in vitro* with two different strains *of Plasmodium falciparu*m, namely chloroquine-resistant Dd2 and chloroquine-sensitive 3D7. The ELISA HRP2 method was used to test the inhibitory effects of the *A. hispidum* extracts alone and in combination with chloroquine. The result exhibited that methanolic extract of the plant has excellent and average inhibitory effects on the growth of 3D7 and Dd2 at 9.2 µg per ml and 2.8 µg per ml of concentrations, respectively. However, aqueous, and EEs of the plant have no antimalarial effect. Dichloromethane (DCM) extract possessed the most potent inhibitory activity; glycosides, flavonoids, coumarins, and antioxidants may contribute to the anti-plasmodial activity. The extract showed low cytotoxicity to HeLa cells (Koukouikila-Koussounda et al., 2013).

60.3.4 ANTI-DIABETIC EFFECTS

In north-western Nigeria, leaves of *Acanthospermum hispidum* are used in curing diabetes mellitus (DM) as a traditional practice. Qualitative and quantitative tests were done with the plant extract. Male Wistar rats were taken for this experiment. Among the five groups of rats taken for experiments, three groups of rats were given the aqueous leaf extract of the plant. Alloxan was used to induce hyperglycemic effects in rats. These diabetic rats were treated with aqueous extract for 28 days with a dose of 3 times (70, 210, 700 mg per kg bw). Results concluded that aqueous extract had reduced the fasting blood glucose level at the same time it improved tolerance of oral glucose at every dose. While giving aqueous extract at the highest dose, i.e., 700 mg per kg, leads to a rise in hepatic glycogen content similar to glibenclamide due to more insulin secretion. As insulin increases, the liver glycogen content by both stimulation of glycogenesis and inhibition of glycogenolysis. Glibenclamide resulted in glucose tolerance administered after two weeks of doses to hyperglycemic rats, whereas this aqueous extract from the leaf gives glucose tolerance right at the first dosage. The results agreed that the aqueous extract of *Acanthospermum hispidum* reduces blood glucose levels and has proven to be antidiabetic (Chika et al., 2018).

60.3.5 ANTI-HELMINTHIC ACTIVITY

Studies were conducted to prove the anti-helminthic activities of *Acanthospermum hispidum* against Indian earthworms *Pheretima posthuma*. For this study, three samples were prepared: control (saline), reference samples (albendazole and piperazine citrate), and leaves extracts. Quantitative tests were conducted in petroleum ether extracts that indicated terpenoids' presence, but hydroalcoholic and chloroform extracts (CEs) showed alkaloids, glycosides, carbohydrates, flavonoids, saponins, and tannins. The anti-helminthic activity was noticed in all the type of extracts. Nevertheless, hydroalcoholic extracts and CEs obtained from the plant have good anti-helminthic activity. Compared to the standard drugs, hydroalcoholic extracts showed better paralytic values and the number of deaths, mainly because of tannins, glycosides, and alkaloids in the leaf extract (Roy et al., 2010).

60.3.6 ANTI-PARASITIC EFFECTS

In the Republic of Benin, aerial parts of the *Acanthospermum hispidum* are used for treating many diseases like malaria as a traditional practice. Two sesquiterpene lactones are separated from *A. hispidum* to check the anti-parasitic activities of the plant. The *in vitro* result suggests that these two lactones have more anti-parasitic activities against *Leishmania mexicana* and *Trypanosoma brucei*. However, crude acidic water extracted with one lactone from the plant showed a weak antimalarial activity *in vivo* against *Plasmodium berghei*. Acute and sub-acute toxicity tests were performed in crude acidic water extract, resulting in no toxicity. The purely separated lactones and crude extract have excellent anti-plasmodial activity, but it has weak antimalarial activity. Acidic water extracts (WEs) of the plant have antimalarial properties by increasing the lifespan of mice by 14 days (Ganfon et al., 2012). *Acanthospermum hispidum* was good at inhibiting *T. brucei* when DCM extracts obtained from the aerial parts of *A. hispidum* were administered (Agunu et al., 2005).

60.3.7 ANTI-TRICHOMONAL ACTIVITIES

Trichomoniasis is a major problem worldwide, lethal to animal and human populations. Nowadays, toxic resistance in available drugs and drug-resistant strains has much more complicated disease treatments. Medicinal plants are the storehouse of bioactive compounds, and it is used as anti-infective agents. A study was made to check the antitrichomonal activities of the

plant. The plant was collected, oven-dried, and ground well. Chloroform, ethyl acetate (EAE), petroleum ether, and MEs were prepared using the Soxhlet extraction method. By vacuum liquid chromatographic technique, the bioactivity of most of the active extract was tested for antitrichomonal activity of the pathogen *Trichomonas gallinae in vitro*. For the treatment of trichomoniasis, non-polar compounds from *A. hispidum* were hypothesized to be more potential agents. Acanthospermal B and sesquiterpene lactones have antibacterial and antimalarial activities. Hence, there is a chance that the antitrichomonal compound of *Acanthospermum hispidum* belongs to the category of sesquiterpene lactones found abundantly in the plant may be effective against trichomoniasis. EAE extract was found to possess antitrichomonal properties in preliminary screening. When associating with standard metronidazole, at 0.16 and 0.36 mg per ml after 48 hrs. and 24 hrs., respectively, the subfraction C7 showed potent antitrichomonal activity with 0.25–0.54 and 0.25–0.66 mg per ml at 48 hr. and 24 hrs. The results indicate that the plant's antitrichomonal compounds were present in the EAE extract in the plant (Adepiti et al., 2014).

60.3.8 ANTICHOLINESTERASE ACTIVITY

Nowadays, memory loss is a significant problem. Traditionally *Acanthospermum hispidum* plant extracts are used in curing memory loss. Generally, in treating neurogenerative disease and memory loss, cholinesterase enzymes like acetylcholinesterase (AChE) and butyrylcholinesterase (Buche) should be reduced by using inhibitors. Many plants have the property to possess anticholinesterase, and it can be verified by using colorimetric assays. An experiment was done to examine the anticholinesterase activity of *Acanthospermum hispidum.* The EAE extract of the plant proved the most significant inhibition to butyrylcholinesterase and AChE with 64.31% and 91.11% concentrations. These results are compared with esterine, which is used as a control (Elufioye et al., 2016).

60.3.9 ANTI-TUMOR ACTIVITY

A study was conducted to identify the role of *Acanthospermum hispidum* in cancer treatment. From the EAE extract of the plant, diterpenes were separated. Dalton's lymphoma cell lines were injected to induce cancer in mice (20–25 g). For this study, four groups of tumor-bearing mice were taken. Median survival time (MST), hematological parameters, histopathology of

tumor cells, and dead cell counts were observed after administering EAE fractions and the solvent extract of *Acanthospermum hispidum*. The results were compared with the control; both fraction and EAE extract have significant tumor controlling properties, concluding diterpenes, the promising source of anti-tumor activity (Rajendran et al., 2007).

60.3.10 ANTI-DIARRHEAL ACTIVITY

MEs of *Acanthospermum hispidum* have proved to have pharmacological properties against diarrhea. When the extracts were administered to the rabbit, there was a smooth muscle relaxation at the low doses, and no effects were seen in the high doses (Agunu et al., 2005).

KEYWORDS

- ***Acanthospermum hispidum***
- **bioactives**
- **antimalarial activity**
- **antidiabetic activity**
- **median survival time**
- **sabouraud dextrose agar**

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CHAPTER 61

Phytochemistry and Bioactive Potential of Galangal [*Alpinia galanga* (L.) Willd.]

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61.1 INTRODUCTION

Alpinia galanga (L.) Willd. (Family: Zingiberaceae), commonly known as galangal, Siamese ginger, greater galangal, Java galangal, blue ginger. "Galangal" word might be originated from a Chinese name which is used for lesser galangal, *"Gao-Liang-Jiang"* that bounded to galanga in Cantonese. Galangal is widely known in Europe for decades even before its botanical origin existed. It is extensively recognized for its significant medicinal properties, and it has also been used as a culinary herb considering its aromatic and peppery taste; In addition, it is used in food by manufacturing industries and by cosmetics and perfumery industries. Galangal is intercontinentally used in countries like India, China, Thailand, Indonesia, Japan, America, and Europe (Chouni and Paul, 2018; Zhou et al., 2018). St. Hildegard of Bingen (1098–1179) portrayed galangal as the "spice of life," that is provided by God to deliver preservation contrary to illness, and it was embraced in numerous Hildegard formulas. Galangal is used to treat countless medical conditions such as treating male infertility, diabetes mellitus (DM), heart disease, gastric cancer, antiallergic, bronchitis, unusual menstruation, antiflatulent, antifungal, anti-itching, stomachaches (Zhou et al., 2018; Hadjzadeh et al.,

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2014; Mazaheri et al., 2014). Galangal has tuber and odoriferous rootstocks that are used for extracting various minor and major chemical components. The galangal is extensively cultivated across India, Indonesia, Vietnam, Southeast Asia, Malaysia, and Southern China. Galangal is believed to have originated in Indonesia, but still, the origin is unclear. The major producer of galangal is India, Indonesia, and Thailand. Its seeking importance is because of its high medicinal oil that is produced from galangal. Thus, this chapter expresses the significance of *Alpinia galanga* and its wide spectrum of this magnificent herb. The usage and applications of *A. galanga* are given in Figure 61.1.

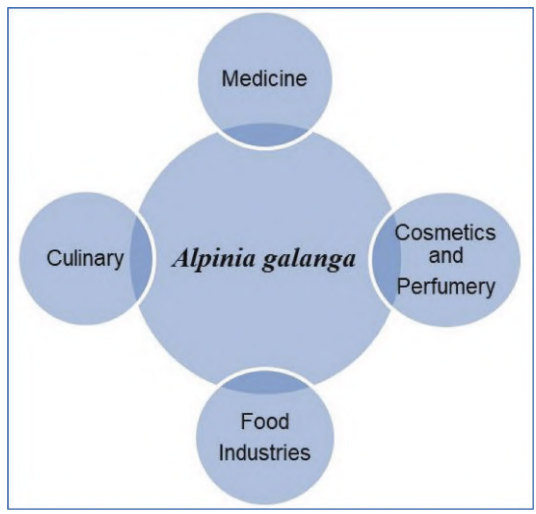


FIGURE 61.1 Applications of Alpinia galanga.

Alpinia galanga is a rhizomatous herb that raises up to 3.5 meters tall; it is perennial clustered, tillering, tuberous root, robust as well; it is extravagantly branched with the ambrosial rhizome. Rhizomes are usually 2.5 to 10 centimeters thick with a reddish brown outward appearance, and light orange within rhizomes. Leaves are oblong-lanceolate 23 to 45 × 6–10 centimeters; glabrous, acute, and ligules are short and rounded. Flowers of galangal are greenish white and fragrant, and the calyx is tubular, claw green, bracteate, bracts are ovate-lanceolate, blade white, corolla lobes oblong, striated with red, shortly 2-lobed at apex, broadly elliptic, panicle ca. 20 × 30 centimeter and the flowering season is from May to August. Fruits are orange-red to wine red that are globose to ellipsoidal capsule 1-to-1.5-centimeter width,

and the wine-red fruits smell matching cardamom; the fruiting season is from September to November (Ravindran et al., 2012; Chouni and Paul, 2018).

61.2 BIOACTIVES

Phytochemical investigations reveal that galangal has rich phenolic compounds and essential oils (EOs) (Zhou et al., 2018). Galangal is analyzed for the major and minor chemical constituents due to its highest medicinal properties. Numerous groups are working on the pharmacological properties of galangal across the globe. To extract the bioactive compounds from *A. galanga* there are a few techniques and methodologies are followed, as mentioned in Figure 61.2 (Namdeo et al., 2015; Das et al., 2020).

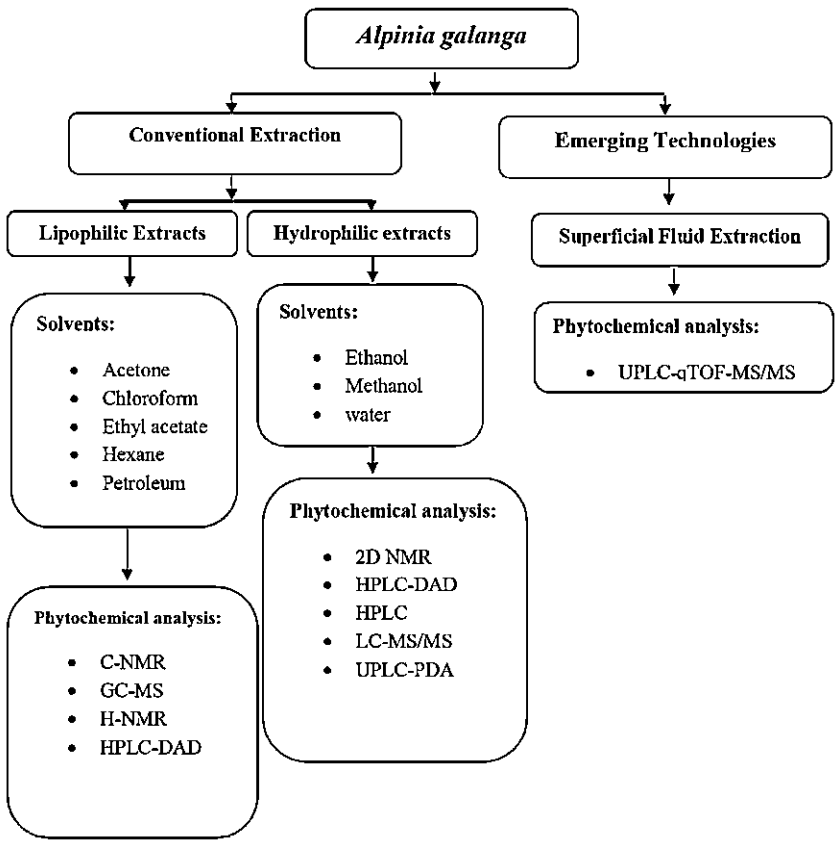


FIGURE 61.2 Conventional extraction procedures and emerging techniques to evaluate *Alpinia galanga*'s chemical constituents.

The seeds and rhizomes of the *A. galanga* are brought to bear as medicine and spices, which attracts researchers across the globe to focus on them. The phytochemical interrogations reveal that *A. galanga* holds numerous phenolic combinations and vital oils. The first reported compound from *A. galanga* is that is excessively present is 1′-S-1′-acetoxychavicol acetate (ACA) (1) (Noro et al., 1988). The compounds detected are p-coumaryl diacetate (2); coniferyl diacetate (3); 1′*S*-1′-acetoxyeugenol acetate (4); and 4-hydroxybenzaldehyde (5). These chemical constituents that were isolated from the plant rhizome are 1′-acetoxychavicol acetate (6); *p*-hydroxycinnamaldehyde (7); (*E*)-8β17-epoxylabd-12-ene-15, 16-dial (8); 1, 7-bis (4-hydroxyphenyl)-1, 4, 6-heptatrien-3-one (9); (BHPHTO) and bisdemethoxycurcumin (10) (BDMC) (Chouni and Paul, 2018). In addition, many chemical constituents that were extracted and isolated from *Alpinia galanga* rhizome such as α-fenchyl acetate (11), α-bergamotene (12), β-farnesene (13), β-pinene (14), β-bisabolene (15), β-Sitosteroldiglucoside (16), β-sitsteryl Arabinoside, camphor (17), methyl cinnamate (18), guaiol (19), and p-hydroxy cinnamaldehyde (20), Three hydroxy-1,8-cineole glucopyranosides, (1R,2R,4S)- and (1R,3S,4S)-trans-3-hydroxy-1,8-cineole, β-D-glucopyranoside. Galangal acetate (21) is responsible for the aromatic flavor that comes from the rhizomes, and the same is determined by GCA (gas chromatography analysis) (Chouni and Paul, 2018; Noro et al., 1988; Aronson, 2016; Someya et al., 2014) (Figures 61.3 and 61.4).

61.3 PHARMACOLOGICAL PROPERTIES OF *ALPINIA GALANGA*

A. galanga holds a wide range of medicinal properties (active ingredients) that is used in traditional medicines, which recently alerted the researchers across the globe to focus on galangal and its curative properties (Zhou et al., 2018). A few instances where the medicinal properties *of A. galanga* have been examined are given in subsections.

61.3.1 ANTIMICROBIAL ACTIVITY

The antimicrobial activity *in vitro* study reveals that the extracts from *A. galanga viz.,* ethyl acetate (EAE) and ether were tested on gram-positive and gram-negative bacteria that are multi-resistant. In the following study, the ether extract is more potent when compared with EAE extract, but both the extract from *A. galanga* shows significant properties against *Klebsiella pneumoniae* and *Staphylococcus aureus* (Shetty and Monisha, 2015). Moreover,

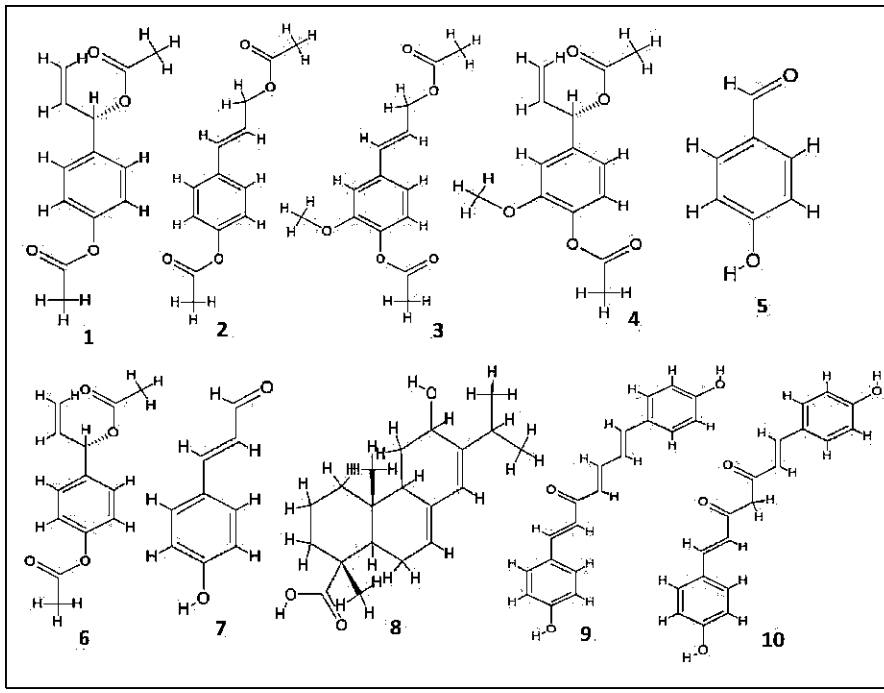


FIGURE 61.3 The chemical constituents present in *Alpinia galanga* are 1′-S-1′-acetoxychavicol acetate (ACA) (1); p-coumaryl diacetate (2); coniferyl diacetate (3); 1′*S*-1′-acetoxy eugenol acetate (4); 4-hydroxy benzaldehyde (5); 1′-acetoxy chavicol acetate (6); *p*-hydroxy cinnamaldehyde (7); (E)-8, β17-epoxy-labd-12-ene-15, 16-dial (8); 1,7-bis (4-hydroxyphenyl)-1, 4, 6-heptatrien-3-one (9); and bis demethoxy curcumin (10).

Source: Chem4Word 2020 Release 9 – (3.1.19.7810) tool was used to draw chemical structures.

it also shows a persistent restraining effect on *Staphylococcus aureus* with MIC at 0.325 mg/mL and MBC (minimum bactericidal concentration) at 1.3 mg/mL (Oonmetta-Aree et al., 2006). In addition, the extracts from *A. galanga* leaves, roots, and rhizomes also show inhibitory activity against numerous pathogens (*Enterobacter aerogenes, Escherichia coli MTCC 1563, Streptococcus epidermis, Salmonella typhimurium, Bacillus subtilis MTCC 2391, Enterococcus faecalis, Klebsiella pneumoniae, Mycobacterium tuberculosis*) (Rao et al., 2010).

61.3.2 ANTI-VIRAL ACTIVITY

The extract of *Alpinia galanga* was tested against HIV (human immunodeficiency virus) type 1 and the rhizome extract showed anti-HIV properties

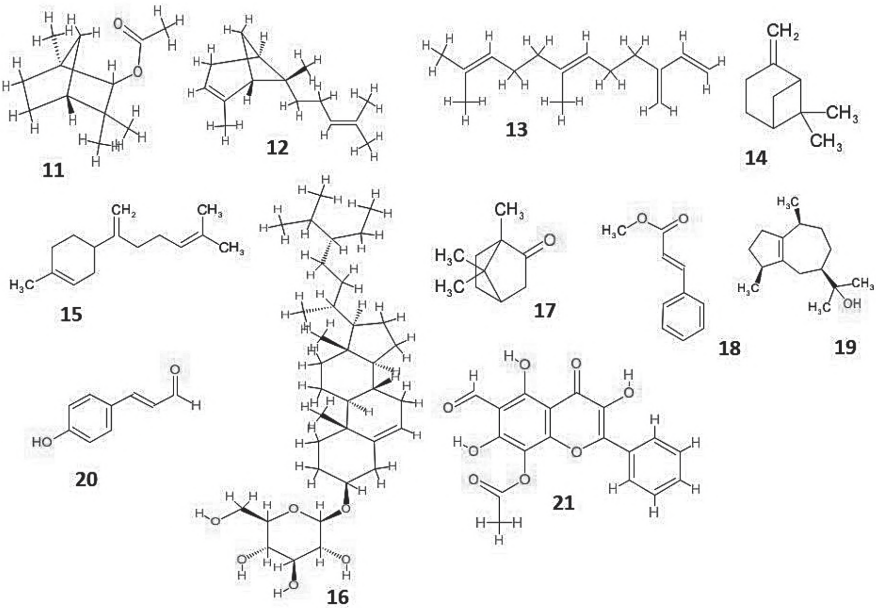


FIGURE 61.4 The chemical constituents present in *Alpinia galanga*: α-fenchyl acetate (11); α-bergamotene (12); β-farnesene (13); β-pinene (14); β-bisabolene (15); β-Sitosterol-di-glucoside (16); β-sitsteryl arabinoside (17); methyl cinnamate (18); guaiol (19); p-hydroxy cinnamaldehyde (20); and galangal acetate (21).

Source: Chem4Word 2020 Release 9 – (3.1.19.7810) tool was used to draw chemical structures.

on obstructing the Reverse Transport by 1′*S*-1′ acetoxychavicol acetate (Yi and Li., 2006). It was administered to the patients who are infected by HIV as a self-medication (Tewtrakul et al., n.d.). Moreover, the root extracts of *Alpinia galanga* efficiency was significantly novel constraining activity on nuclear exportation of Rev and Rev-exportation action (Tamura et al., 2009). The chemical constituents of *Alpinia galanga*, when combined with other antiviral drugs, can be a new combination that can be a considerable game changer in treating HIV contagion (Trimanto et al., 2021).

61.3.3 ANTICARCINOGENIC ACTIVITY

In recent time studies have shown that the extracts of *Alpinia galanga* has anticancer properties against various cancer cell lines. The extract of *Alpinia galanga* inhibits PC-3 cell growth, it also demonstrated antiproliferative activity in MCF-7 breast cancer cell lines by initiating S-phase cell cycle seize followed by apoptosis (Suja et al., 2008). Furthermore, the extracts efficacy

was also tested on the L929 (conventional mouse fibroblast cells) and human gastric adenocarcinoma cell lines *in vitro* (Hadjzadeh et al., 2014). The ethanolic constituents of *Alpinia galanga* were showing promising results like antiproliferative and initiation of programmed cell death activities when tested on the human breast carcinoma cell line (Samarghandian et al., 2014).

61.3.4 IMPACT ON THE NEUROPROTECTIVE ACTIVITY

The fractions of *A. galanga,* such as chloroform, *n*-hexane, and EAE, act against Alzheimer's disease in the dose of 200 as well as 400 mg/Kg in Alzheimer's disease-induced mice. Chloroform constituent demonstrated exceptional neuroprotective in Alzheimer's sort of hypomnesia triggered by amyloid β (25–35). The considerable chemical constituent ACA is believed to act as a treating agent for amnesia caused by Alzheimer's. The EAE and methanolic extract have phenomenal stimulant activity on CNS (central nervous system) (Singh et al., 2011).

61.3.5 ANTI-ULCER ACTIVITY

The effects of *Alpinia galanga* extract on experimentally induced stomach ulcers in rats have been examined. The measure of stomach mucosal injury caused by pyloric ligation and hypothermic restraint stress in rats significantly reduces at a dose of 500 milligrams per kilogram BW of the ethanolic extract (EE). The test results reveal that *A. galanga* has a powerful antisecretory and cytoprotective action, which may be accountable for its antiulcerogenic action (Al-Yahya et al., 1990). The strong antiulcer principles 1′- and 1′-acetoxyeugenol acetate and acetoxychavicol acetate were isolated from the seeds of *Alpinia galanga* and produced synthetically (Mitsui et al., 1976). The implications of 1′S-1′-acetoxychavicol acetate and linked phenylpropanoids separated from the root systems of *Alpinia galanga* on ethanol-induced intestinal ulcers in rats were researched. It was found that 1′S-1′-acetoxyeugenol acetate and 1′S-1′-acetoxychavicol acetate repress ethanol-induced intestinal mucosal ulcers (Matsuda et al., 2003).

61.3.6 ANTI-DIABETIC ACTIVITY

In rabbits, extracts from the roots of *Alpinia galanga* had anti-diabetic properties on blood sugar content. Finely ground roots extracted with methanol and

water infusions dramatically reduced sugar levels in normal rabbits (Akhtar et al., 2002). In both euglycemic and diabetic rats, methanolic extract of aerial portions of *Alpinia galanga* proved efficient in regulating diabetes and improving serum lipids (Verma et al., 2015). Methanolic preparations of *Alpinia galanga* significantly inhibit the glycosylation of hemoglobin. The plant extract suppresses the actions of both α-glucosidase and α-amylase in a dosage-dependent mode, indicating that the plant has significant *in vitro* anti-diabetic properties (Heera et al., 2014).

KEYWORDS

- **acetoxychavicol acetate**
- ***Alpinia galanga***
- **galangal**
- **glycosylation**
- **minimum bactericidal concentration**
- **Zingiberaceae**

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CHAPTER 62

An Overview of Bioactive Constituents and Pharmacological Activities of Annatto (*Bixa orellana* L.)

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62.1 INTRODUCTION

Bixa orellana of the Bixaceae family is a small evergreen and dicotyledonous plant commonly known as achiote, a Mexican word meaning shrub and *"Latkan"* in Bangladesh (Shilpi et al., 2006). Brazil is its origin, and it grows in tropical countries between Central America and the south, such as Mexico, India, East Africa, Peru, Indonesia, Kenya, and Ecuador (Vilar et al., 2014; Chandel et al., 2014). *B. orellana* is a versatile industrial crop. The leading industrial generators and the main production areas are the tropic nations, Mexico, Jamaica, Peru, Philippines, Kenya, and Brazil (Corrêa, 1978). Approximately 80% of the global product, around 11,000 tons of seeds/annum, is used by Western European countries and the USA. It is concocted and utilized to confer distinctive orange-yellow shades to milk products (Voeks and Leony, 2004). *Bixa orellana* L., also identified as annatto, symbolizes the Amazonian races, traditionally employing annatto seed extract as paint stained to decorate their bodies during divine rituals (Coelho-Ferreira, 2009). Furthermore, it is assumed, the authentic Aztec chocolate drink has cocoa in addition to annatto seeds (Parra and Fidalgo, 2010). Achiote, a fruiting shrub, grows roughly about 1.8–6 meters having approximately 5–15 cm long and 4–11 cm wide pointed leaves. Flowering happens in vertical upstanding groups, flashy, white or pink shades with five petals. Flowers of *B. orellana* are characterized as bisexual; possess five sepals. Fruit is 5 cm long, ovoid,

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spiked, and bivalved (Chandel et al., 2014). Mature seeds are gathered during February. Globally, 70% of the coloring agent is extracted from *B. orellana*. Annatto, an essential colorant used in cultural contexts for a red-orange pigment, is in the arils around the seed, which is used in textiles, paints, and cosmetics. Initially, it was utilized as a food colorant in the name of paprika and later spread into many sectors of industries (Moreira et al., 2015). It has wider folkloric use in India, the Philippines, China, Guiana, and Brazil (Shilpi et al., 2006). Leaf concentrates have been utilized for a long time as restorative and folkloric solutions to treat cerebral pain, diarrhea, fever, different microbial infections, acid reflux, obesity, snakebites, astringent, as natural lip paint and to treat different skin conditions in the traditional medicinal system (Chandel et al., 2014). In industrialized countries, the name "annatto" is usually connected to seed extract of *B. orellana* holding carotenoid-kind dyes, extensively utilized in textiles, tinting groups of foodstuffs, and cosmetic products (Carvalho and Hein, 1989). Lately, *B. orellana* essences are feasible, economical, and alternatively exploited for artificial colorants and dyes in the finishing and dyeing of leather products (Selvi et al., 2013). *B. orellana* root and leaf infusions are utilized in Trinidad and Tobago to treat diabetes, hypertension, and jaundice; extracts of leaves exhibit broad antimicrobial, antioxidant, antidiarrheal, analgesic, and hypoglycemic activities (Stohs, 2014). It is a well-known reality that most of the plant parts of *B. orellana* are used in conventional medication to treat various diseases (Camargo, 1985). In Brazil, *B. orellana*, the extract of seed, roots, and leaves, are famous as an aphrodisiac medication and a solution to parasitic diseases, heal fevers, and inflammatory conditions. The whole plant is utilized to treat diarrhea. The whole plant infusions counteract poisoning due to *Hura crepitans* L., *Jatropha curcas* L., and *Manihot esculenta* (Crantz) (Di Stasi et al., 1989). A warm infusion of leaves is used to arrest nausea and vomiting, a moderate diuretic, negotiates heartburn, prostate issues, urinary complications, and stomach ailments (Camargo, 1985).

62.2 BIOACTIVES

Phytochemical examinations have exposed *B. orellana* bearing around 25 biochemical compounds from various infusions, resulting in significant ingredients: carotenoids, carbohydrates, proteins, steroids, terpenoids, flavonoids, tannins, phenolics, alkaloids, and glycosides discovered alone in the leaves, anthraquinones alone in seeds (Fleischer et al., 2003). A crude protein extract is obtained from *B. orellana,* known as annatto; it consists of a fat-soluble

bixin, a hydro-soluble norbixin and other carotenoids (Raddatz-Mota, 2017). The predominant component is geranylgeraniol, representing 1% of the dry seed weight. Norbixin is another demethylated ingredient of bixin; due to its saponification (Vilar et al., 2014). The norbixin and bixin carotenoids are well-known compound constituents of seeds and are accountable for extracts' yellow, orange, and red pigmentation. Moreover, seed extracts of achiote have about 107 compounds; experimentally, many compounds are yet to be characterized (Stohs, 2014). Two carotenoids of annatto provide freakish red color: norbixin and bixin. Methyl (9-cis)-hydrogen-6,6-diapo-W, W-carotenedioate; Bixin) is the principal compound accountable for the orange-red color from seeds and infusions of *B. orellano* is responsible for roughly 80% of its cumulative carotenoids (Carvalho and Hein, 1989; Parra and Fidalgo, 2010). The seed extracts consist of 40 to 45% cellulose, up to 5.5% sugars, 0.3 to 0.9% necessary oils, 3% fixed oils, 1.0 to 4.5% pigments, and 16% proteins and alpha and beta-carotene, minor amounts of tannins and saponins (Vilar et al., 2014). Globally, the economic importance of annatto has significantly been recognized as it is used in cosmetics, food, and pharmaceutical industries; it is practically non-toxic and does not alter flavor foodstuff. This carotenoid-rich dye generates attractive colors (dark red and yellow) that aid in making dairy products (margarine, butter, cheese), meats, paint, soaps, fabric colors, lacquer, nail polish, and others. Apocarotenoids present in smaller amounts is bixin dimethyl ester, norbixin, and by-products of lycopene degradation (Raddatz-Mota, 2017). *B. orellana* is demonstrated to possess a reliable reservoir of antioxidants. A study was intended to examine the unstable bio-active compounds' characterization of *B. orellana* dehydrated seeds, young fruits, bark, sapwood, and leaves examined using GCMS coupled with Headspace solid-phase microextraction methods. α-humulene is the principal gaseous compound in *B. orellana* seed extract, accompanied by caryophyllene, γ-elemene, and D-germacrene. Gaseous compounds identified in *B. orellana* extracts possess mainly monoterpenes, arenes, and sesquiterpenes (Giorgi et al., 2013). The bioactive compound derived from annatto exhibits antimicrobial and antioxidant properties. In the phytochemical analysis of Bixa seeds versus leaves, alkaloids were detected in parts of leaves but not in seeds, while anthraquinones were distinguished in seeds, not in leaves (Selvi et al., 2011). The chemical structures of significant annatto are given in Figure 62.1.

Compounds including β-cryptoxanthin, geranylgeraniol, lutein, procyanidin B2, procyanidin B3, tannin isomer and ellagic acid deoxyhexose are found to inhibit pathogenic organisms, namely bacteria, fungi, viruses, and some protozoans. Furthermore, eight apocarotenoids were isolated from annatto seeds:

methyl 1 (all-E)-apo-8-lycopenoate, dioate, 6-geranylgeranyl 6-methyl-(9Z)-6, 6-geranylgeranyl-6-methyl-6-6-diapocaroten-6-6-dioate, 8 diapocaroten-6-8,6-geranylgeranyl-8-methyl-6,6-diapocaroten-6-6-dioate, methyl (all-E)-8-apo-beta-carotene-8-oate, methyl (all-E)-apo-6-lycopenoate and methyl (7Z, 9Z, 9Z)-apo-6-lycopenoate, methyl (9Z)-apo-8-lycopenoate (Vilar et al., 2014).

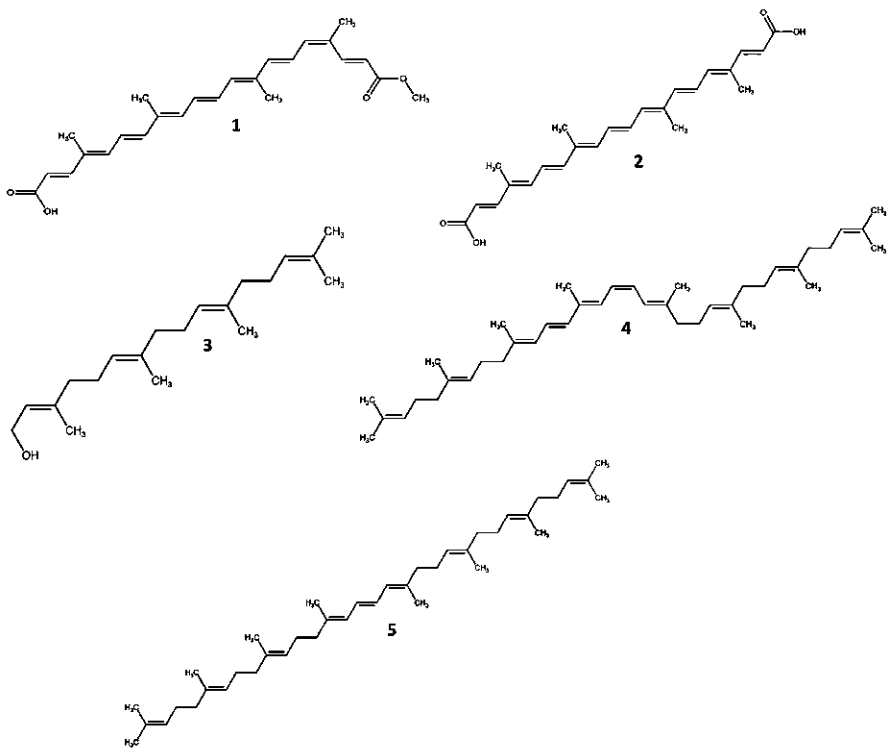


FIGURE 62.1 The chemical structures of few essential oil carotenoids of *Bixa orellana.* (1) Bixin (Z bixin or cis bixin); (2) norbixin; (3) geranylgeraniol; (4) phytofluene; and (5) phytoene.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

In aqueous and organic extracts of *B. orellana*, more than 100 volatile compounds have been detected; of these, 50 have already been identified where (+)-cyclosativene, copaene, isoledene, ∝-cubebene, bornyl acetate, 1-heptanetiol, seline-6-en-4-ol,δ-selinene, ∝-caryophyllene, γ-elemene, β-humulene, geranyl phenylacetate, (–)spathulenol, (+)-ylangene, and

3-methylpyridine, β-pinene, 4-methylpyridine (Vilar et al., 2014). *Bixa orellana* also helps as an anti-inflammatory agent in treating pulmonary diseases (Neto et al., 2020). The chemical structures of some carotenoids and apocarotenoids derived from annatto seeds, organic extract, and leaves are given in Figure 62.2.

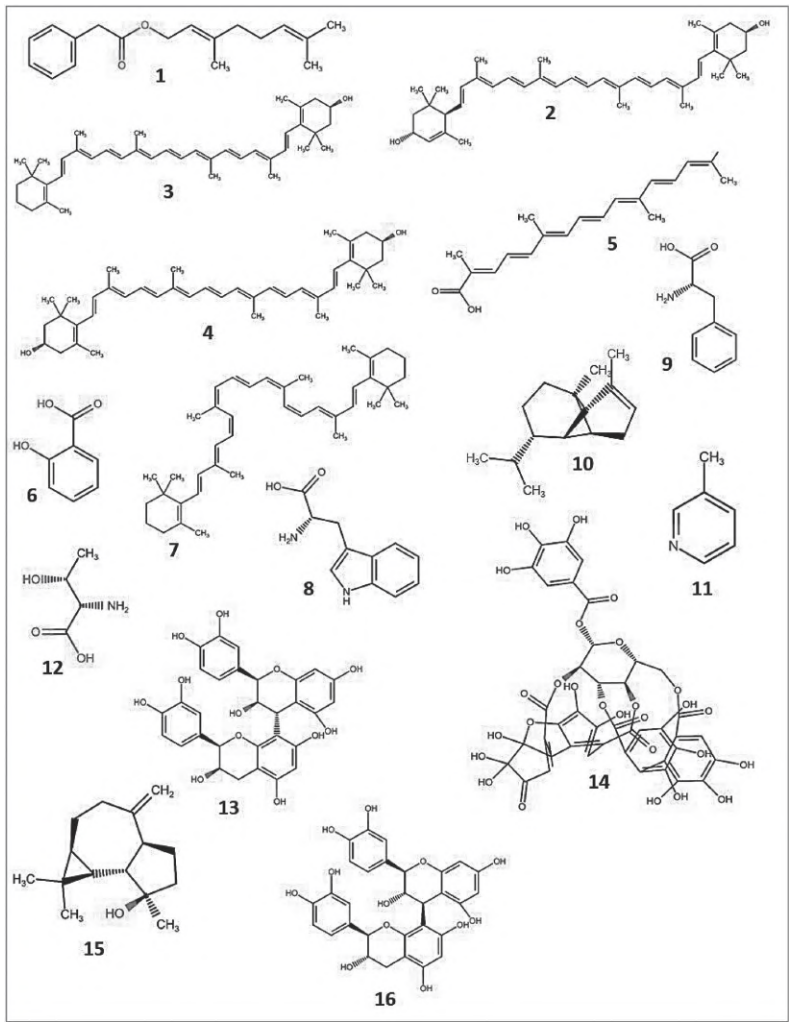


FIGURE 62.2 The chemical structure of bioactives of *Bixa orellana*. (1) Geranyl phenylacetate; (2) lutein; (3) cryptoxanthin; (4) zeaxanthin; (5) crocetin; (6) salicylic acid; (7) beta-carotene; (8) tryptophan; (9) phenylalanine; (10) copaene; (11) 3-methyl pyridine; (12) threonine; (13) procyanidin B2; (14) granatin B; (15) (–)-Spathulenol; and (16) procyanidin B3.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

62.3 PHARMACOLOGY

Experimental evidence of *B. orellana*'s pharmacological activities is copious nowadays, especially concerning leaf and seed extracts. Antidiabetic, anti-convulsant, cardioprotective, and anti-microbial activities of *B. orellana* extracts have been documented (Patnaik et al., 2011; Asokkumar et al., 2012; Selvi et al., 2011). Moreover, some pharmacological studies have revealed that *B. orellana* essences hold anthelmintic and antiprotozoal action (Barrio et al., 2004). Prefatory observations on repellency upon *A. aegypti* of 3 assorted dehydrated seed essences (ethanol/water), ethanol, and hexane registered a notable skin shielding action. Protection of 73% and 90% for hydro-ethanolic and hexane extracts was recorded (Giorgi et al., 2013).

62.3.1 ANTIMICROBIAL ACTIVITY

Various studies concerning leaf extracts of Bixa has investigated specific antimicrobial characteristics *in vitro*. These investigations revealed that leaf infusions manifest a broad spectrum of antifungal and antibacterial actions. The initial studies (Irobi et al., 1996; Castello et al., 2002; Fleischer et al., 2003; Gomez et al., 2012) confirmed that ethanolic infusion of leaves displayed antimicrobial activity upon *Pseudomonas aeruginosa, Bacillus* spp., *Streptococcus faecalis* and *Staphylococcus aureus* (gram-positive organisms) while exercising limited action toward *Escherichia coli* (a gram-negative organism) and the fungi *Aspergillus niger* and *Candida albicans*. Those outcomes meant that Bixa extracts manifested action against gram-negative and gram-positive bacteria along with fungi. The value of an ethanolic leaf extract of Bixa has been recommended as a food preservative (Gomez et al., 2012). More lately, Silva et al. (2010) proposed that freeze-dried hydroalcoholic Bixa leaves extracts showed remarkable inhibition upon *Proteus mirabilis* and *P. aeruginosa* with moderate action upon *Bacillus cereus* and *Staphylococcus aureus*, and weaker action upon *Salmonella typhimurium*. The leaf infusion manifested feeble activity toward *Mycobacterium tuberculosis.* A lukewarm H_2O distillation of leaves of Bixa has excellent antimicrobial action upon *Shigella dysenteriae* and *Streptococcus* species with moderate action towards *E. coli* (Ul-Islam et al., 2011).

Cryptoxanthin, the phytochemical extracts from seeds and leaves of *B. orellana,* shows antimicrobial properties against *Proteus vulgaris, Salmonella typhimurium, Staphylococcus epidermidis* and *Staphylococcus aureus*

(Barbieri et al., 2017). Geranylgeraniol acts against *Mycobacterium tuberculosis* (Vik et al., 2007), *Leishmania amazonensis* (Lopes et al., 2012) and *Mycobacterium tuberculosis* (Montero et al., 2004). The chemical Lutein is microbicidal to *Listeria monocytogenes*, *Aspergillus niger, Trichophyton mentagrophytes,* and *Candida albicans* (Ciro et al., 2014). Procyanidin B2 and Procyanidin B3 are antimicrobic to *Porphyromonas gingivalis* (Neto et al., 2020), respectively. Ellagic acid deoxyhexose shows antimicrobic reaction towards *Staphylococcus aureus*, *Pseudomonas aeruginosa,* and *E. coli* (Raga et al., 2011). Consequences of the antibacterial screening show that *Bixa orellana* methanolic leaves concentrate inhibit the activity of dysenteric and diarrheal diseases causing microbes *viz., Staphylococcus aureus, Shigella dysenteriae* and *E. coli* (Shilpi et al., 2006). Hydro-concentrates of leaves presented excellent antimicrobic action against *Shigella dysenteriae, Streptococcus* species, and against *E. coli* (Stohs, 2014). The polar infusions from *B. orellana* have been lately recommended as safe, organic natural preservatives in food forms because of their antioxidant and broad-spectrum antibacterial actions (Viuda-Martos et al., 2012).

62.3.2 ANTI-INFLAMMATORY ACTIVITY

A study aimed to examine bixin's possible antinociceptive and anti-inflammatory effect in preclinical models for acute pain and inflammation: carrageenan-effected paw edema and the myeloperoxidase (MPO) activity in male Wistar rats was determined using bixin (15 or 30 milligrams per kilogram through oral feeding). The antinociceptive influence of bixin was estimated using formalin and hot plate analyzes in rat models and the acetic acid-provoked writhing test in albino mice models (27 or 53 milligrams per kilogram); locomotor action was assessed by open field test. Bixin significantly lowered the MPO activity and the carrageenan-provoked paw edema and increased the hot plate's latency time. Bixin significantly lessened the quantum of flinches in both stages. The quantity of acetic acid-provoked writhings and formalin examination without altering the locomotor action in the open field test; the investigation confirms the effectiveness of bixin as an anti-inflammatory channel tool linked to reducing the neutrophil migration. Moreover, the antinociceptive attribute of bixin does not induce a sedative effect (Pacheco et al., 2019). The leaf extract of achiote showed anti-inflammatory properties against chronic and acute inflammations and was justified by showing suppressed inflammatory markers (Neto et al., 2020). The water-based Bixa leaf extract exhibited remarkable anti-inflammatory

factors toward severe and prolonged soreness in rats (Zuraini et al., 2007). Intense inflammatory responses were provoked in rat paws through histamine, carrageenan, bradykinin, and serotonin were repressed by the oral treatment of 50 milligrams per kilogram and 150 milligrams per kilogram of extract. Persistent soreness was provoked by implanting cotton beads into the sides of animals. Daily oral administration of 150 milligrams per kilogram of extract exhibited meaningful repression of infection. The capacity of a lyophilized fluid concentrate of Bixa leaves to restrain bradykinin-initiated aggravation was affirmed (Stohs, 2014). It decreased nitric oxide (NO) production confirming anti-inflammatory activity (Keong et al., 2011). The counter inflammatory action of aqueous achiote was assessed utilizing serotonin-initiated edema in rats; results indicate bixa extract enhanced peritoneal vascular penetrability (Neto et al., 2020).

62.3.3 ANTIOXIDANT ACTIVITY

Several study groups confirmed the antioxidant and reactive oxygen species (ROS)' mitigating activities of Bixa leaf extracts (Ul-Islam et al., 2011; Viuda-Martos et al., 2012; Conrad et al., 2013). Viuda-Martos et al. (2012) recorded that ethanolic leaf extracts of Bixa displayed notable antioxidant action using five separate assay methods. Conrad et al. (2013) observed that ethanolic Bixa plant extracts restrained ROS provoked lipid peroxidation (LPO), decreased glutathione (GSH) levels, and enhanced catalase (CAT) action in CCl_4-treated rats. The antioxidant action of β-cryptoxanthin was assessed in non-alcoholic fatty liver illness. There was a significant decrease in lipogenesis β-oxidation and LPO, which shows a defensive reaction in steatohepatitis and cirrhosis. Besides, β-cryptoxanthin obstructed macrophage polarization, expanding the polarization for macrophages M2 and decreasing the polarization for macrophages M1 (Louro and Santiago, 2016). The ethanol concentrates of Bixa leaves displayed critical cancer prevention action reliant on five distinctive study frameworks. Ethanol concentrates of achiote plants restrained LPO, improved hepatic, and blood conditions, lessened GSH level and enhanced CAT response in treated rodents. The methanol concentrate of Bixa leaves exhibited hepatoprotection in animal models from carbon tetrachloride. A portion of 500 mg/kg body weight of the concentrate given multiple times checked CCl_4 of liver cholesterol (53%), aspartate aminotransferase (57%), and alanine aminotransferase (52%). The results are supported by histopathological examination of liver tissues (Stohs, 2014).

62.3.4 IMMUNOMODULATION ACTIVITY

The effects of conjugated linoleic acid (CLA) and lutein on broiler chickens' immune response and growth performance were evaluated in the absence and presence of Salmonella lipopolysaccharide (LPS) immune trial. That study showed CLA decreased growth performance, but lutein prevented this adverse effect (depending on CLA dose). Lutein has an anti-inflammatory effect, and 2% of CLA supplementation improved the humoral immune response (Neto et al., 2020).

62.3.5 CYTOTOXIC ACTIVITY

Knowing the phytochemical aspects of medicinal plants helps us understand the plants' toxic nature and prevents humans from pant-induced toxicity. The cytotoxicity of *B. orellana* extract against B16F-10 melanoma cell lines was investigated. *B. orellana* extracts enhanced the quantum of cell mortality; this was obvious by the MTT test evidenced by morphological studies. The control cells showed nuclei with uniform chromatin distribution, while the chromatin amount was less in *B. orellana* extract-exposed cells and morphological changes were apparent during apoptosis. Fluorescence microscopy examination uncovered that the *B. orellana* extract actuated apoptosis and caused morphological changes in cells. DNA fragmentation studies affirmed the characteristic of apoptosis. Gerangeraniol from *Bixa orellana* seed extract is known to be lethal against *Leishmania amazonensis* (Lopes et al., 2012). Trans-geranylgeraniol squalene and β-sitosterol are reported to possess anticancer activity on B16F-10 melanoma cell line (Kumar and Periyasamy, 2016).

62.3.6 NEUROPHARMACOLOGICAL AND ANTICONVULSANT ACTIVITY

Pharmacologic studies were performed with a partly filtered hydro-infusion of the *Bixa orellana* roots. Experiments revealed that the infusion offers a depressant impact on voluntary movement without undermining spontaneous action. In a Rolling Roller Activity test conducted to assess the neurotoxicity, the hydro-extract's toxicity is not witnessed till the fatal dosage limit is attained. In contradiction to the above result, the ED60 treatment of the H_2O infusion of *Bixa orellana* did not display CNS depression (Dunham and Allard, 1960). The methanol concentrate of *Bixa orellana* leaves was

explored whether it impacts the sensory system and controlling seizures. Various experiments were appropriated to assess anticonvulsant and neuropharmacological effects. The neuropharmacological activity was examined by employing the pentobarbitone-actuated hypnosis in open-field and open cross-tests. Pentobarbitone was given at an apt dosage, which actuates hypnosis in test animals, activating the gamma amino-butyric acid (GABA) (McNamara, 1996). When *B. orellana* leaf extract was administered, it induced calming effects on the CNS. Epilepsies are a disorder of neuronal sensitivity characterized by unusual and rapid seizures. The anticonvulsant movement was monitored by an anticonvulsant test employing strychnine. The result extended endurance time after strychnine administration comparable to the control. *Bixa orellana* extract displayed a reduction in locomotor movement in animal models (Aktary et al., 2020). Intraperitoneal applications of 20 milligrams per kilogram of the hydro extract did not potentiate pentobarbital-provoked nap time in mice. Swinyard's techniques employing pentylenetetrazol and electroshock were employed in examining the hydroextract for anticonvulsant characteristics. A dosage of 100 milligrams per kilogram in mice did not modify the convulsions presented, symbolizing the nonexistence of anticonvulsant action (Dunham and Allard, 1960).

62.3.7 DIURETIC ACTIVITY

Diuretics are medications that intensify the pace of urination. There are a few classes of diuretics, and they enhance the discharge of water from the body by acting through various mechanisms. An attempt was made to survey the capacity of native plants for their diuretic action; urine volume, sodium, potassium, and chloride levels in urine appropriating standard strategies. From the results, methanolic concentrates of achiote leaves possess significant diuretic action by increasing urine yield and increased exudation of sodium (Na), potassium (K), and Chloride (Cl) levels. However, the action was not similar to the quantitative response elicited by the standard diuretic drug. Hence, isolating bioactive constituents from *B. orellana* will be a therapeutic benefit (Radhika et al., 2010).

62.3.8 HYPOGLYCEMIC ACTIVITY

The hypoglycemic action of *Bixa orellana* was estimated. The extract, when offered 15 minutes after loading glucose, methanolic infusions of *B.*

orellana displayed notable hypoglycemic actions utilizing a revised oral glucose endurance experiment with Swiss Webster mice as experimental models. An infusion of *B. orellana* was found to lessen blood glucose levels when administered 45 min before glucose load (Quanico et al., 2008). A few investigations support that concentrates of achiote display moderate hypoglycemic activity. The hypoglycemic action of methanolic hydro leaves concentrates of *B. orellana* were investigated. The extracts are given 45 min before a glucose load wanes blood glucose level by 30%. The ME produced a 19% reduction in glucose levels when given 15 minutes before, with 520 mg/kg oral dosage (Stohs, 2014). A methanol concentrates of leaves showed modest inhibitory action *in vitro* against α-amylase (Ponnusamy et al., 2011), which would slow glucose absorption in the gastrointestinal tract (Stohs, 2014).

62.3.9 ANTI-HISTAMINIC ACTIVITY

Bixa orellana extract from leaves possesses anti-inflammatory properties. Histamine is one of the inflammogen that appends to intense irritation and increase of vascular expansion. Paw edema studies; is a valid measure for exploring agents with anti-inflammatory capacities. The examination shows that the openness of rodent's paws to histamine results in the accumulation and movement of fluid in tissues in the exposed area, an event that prompts tissue enlarging. The decreased paw volumes and permeability of peritoneal vascular normalization were aided by suppressing other permeability-regulating substances (NO and VEGF); thus, revealing Bixa extracts antihistamine activity. The Evans blue color test reflects the reduction of expanded vascular penetrability (Yong et al., 2013).

62.3.10 GASTRIC DISCHARGE AND INTESTINAL MOVEMENT ACTIVITY

The influence on unincited gastric discharges was investigated. *B. orellana* infusions were jabbed intraduodenally with a dosage of 400 milligrams per kilogram during pyloric ligations. The infusion of *B. orellana* was administered hung in 2% tragacanth, and the standard treatment involves relative values of the suspending agent alone. After five hours of the procedure, the creatures were decreased, and the gastric fluid was obtained. The total root infusions and their portions restrained the quantity of gastric discharge.

Nevertheless, only the complete root extract and its alcohol portion influence acidity (Dunham and Allard, 1960). The impact on Intestinal movement was studied *in-vitro*. Sections of ileum from the guinea pig model were dangled in an aerated dip of 50 milliliters of Tyrode's liquid at 38°C. The involuntary confinements were read kymo-graphically. Adding 50 or 100 mg of the H_2O extract reduced tonus and a recess of contractions. After a minute, the frequency and amplitude of contractions recovered to routine; however, the tonus was reduced in 100 mg Bixa treatment. A similar pattern was noted when additional dosages when appended to the bath (Dunham and Allard, 1960). The antiulcer influences of water and ethanol-based leaf extract of Bixa were confirmed in rats (Huamán et al., 2009). Dosages of 200 and 400 milligrams per kilogram presented partial gastro-guarding impacts toward 96% ethanol-influenced damage and lessened movement of pro-inflammatory cells.

62.3.11 ANTICANCER ACTIVITY

Negotiating cutaneous melanoma is considerably complicated as it displays significant resistance to conventional treatment procedures as they have an extraordinary capability to metastasize. An exciting option for sensitization of tumor cells to chemotherapy is the blend of traditional drugs with cytostatic entities of moderate toxicity. In an experiment, the impact of bixin, a copious apocarotenoid found in *Bixa orellana* was evaluated on (A2058) human melanoma cells to dacarbazine therapy, an anticancer drug used clinically to treat metastatic melanoma. Two novel apocarotenoids: 6,7′-diapocarotene-6,7′-dioic acid and 6,8′-diapocarotene-6,8′-dioic acid were identified through UPLC-DAD-MS/MS investigations of *B. orellana* seed bioactive extracts. Bixin (*Z*-bixin) was assessed on A2058 cells showing the carcinogenic BRAF VE600 variation and immunity to dacarbazine therapy. Bixin lessened cell emigration, encouraged tumor repression, provoked cell cycle interruption in the G2/M phase and apoptosis. When linked with dacarbazine, bixin sensitized A2058 cells to chemotherapy, intensifying its pro-apoptotic effects, antiproliferative, and anti-migratory properties. Blended therapy further provoked increased MDA (malondialdehyde) and ROS generation than monotherapy, implying bixin's increased oxidative stress production contributed significantly to sensitizing A2058 cells. Hence, Bixin exercises inherent anti-melanoma action by mechanisms equivalent to dacarbazine, boosting its effectiveness

in blended treatment for cutaneous melanoma (de Oliveira Júnior et al., 2019).

62.3.12 HYPOTENSIVE ACTIVITY

Influences of *Bixa orellana* on blood pressure were studied. The animals were anesthetized by the intraperitoneal treatment of pentobarbital sodium (50 milligrams per kilogram). The cannulated carotid artery was attached to a mercury manometer with polyethene lining loaded with a heparin solution under normal saline. Water extract of Bixa was administered inside the femoral vein. Portions of 10 and 25 milligrams per kilogram ended in momentary drops in blood pressure. Nevertheless, doses of 50 and 100 milligrams per kilograms produced drops in blood pressure 40% of standard and persisting for 30 minutes on an average. The blood pressure later steadily progressed and reached regular at 90 minutes (Dunham and Allard, 1960).

62.3.13 HEPATOPROTECTIVE ACTIVITY

There is an accelerating trend of liver malfunction and a paucity of efficient medications for liver ailments. In an investigation to whether the hydro/ethanolic leaf extracts of *B. orellana* L. possess liver protective action towards CCl_4 provoked Liver damage in mice animal model. A 0.5 g/kg BW dosage was recognized from the toxicity test and offered to albino mice. Histological studies of the liver assessed the degree of hepatic impairment. Hydro/ethanolic leaf distillations of Bixa does not show any toxicity up to two grams per kilogram BW. in mice. Prior administration of CCl_4 for seven days significantly restricted serum ALT and AST levels, with tissue sections conclusions manifesting a shielding impact on the liver cells. Hence, *B. orellana* has strong hepatoprotective action toward oxidative impairment (Lopez et al., 2017).

62.3.14 ANTIVENOMOUS ACTIVITY

Various traditional medicines of plant origin are used to treat poisonous serpent bites; numerous investigations have explored the value of ethanolic leaf distillations of Bixa to counterpoise snake toxin and check

associated negative influences. Extracts of Bixa conferred to afford partial shield toward edema forming action and mortality in rats toward *Bothrops asper* and *Bothrops atrox* venom (Otero et al., 2000a, b; Núñez et al., 2004).

62.3.15 SAFETY CONCERNS OF BIXA ORELLANA

Even though Bixa leaf infusions and macerated leaves have been used for ages to treat numerous therapeutic targets, limited data concerning well-devised and safety issues are acknowledged; numerous toxicity and subacute toxicity investigations have been published on infusions of seeds of Bixa (annatto); hence outcomes of those investigations may not be extended to leaf essences as both parts have considerably diverse chemical ingredients. The common informational safety evaluation of Bixa leaf involved the placebo-included, double-blind, randomized investigation of Zegarra et al. (2007), by using 250 milligrams of homogenized leaves thrice daily for 180 days. The investigation enlisted 68 cases in both treatment and check groups, with roughly 55 individuals making every group. Discrepancies were not observed in the occurrence of unfavorable effects informed by the subjects among the treatment and placebo groups. Severe antagonistic outcomes were not recorded. The occurrence of constipation was recorded in roughly 3% of the members involved in the study, which hardly restrained them from staying in the study. The exclusive safety investigation published in animals included offering leaf extract of Bixa with measures to the tune of 120 milligrams per kilogram extending for seven days to rat models (Abatan, 1990). The researcher recorded an improvement in absolute RBC numbers and packed cell quantity and subtle variation in leukocyte number/hemoglobin at dosages of 80 milligrams per kilogram and 120 milligrams per kg. A reduction in albumin content and rise in chloride, sodium, and potassium content in blood; increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) actions. The investigation, as mentioned above, has not been replicated, and on the contrary, conflicting results have been noted in different animal investigations. The basis for this contrariety is not known so far (Stohs, 2014).

KEYWORDS

- **achiote**
- **annatto**
- ***Bixa orellana***
- **bixin**
- **cytotoxic activity**
- **reactive oxygen species**

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CHAPTER 63

Medicinal and Bioactive Properties of Red Hogweed (*Boerhavia diffusa* L.): An Overview

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63.1 INTRODUCTION

Diseases are spreading and evolving new as humans evolve, so to control or cure these diseases, many medications are taken worldwide, which will again cause side effects and ultimately be dangerous to humanity. So, to prevent that, bioactive compounds derived from medicinal plant extracts can be used. *Boerhavia diffusa* L. is one among the therapeutic plants used in ayurvedic and Unani medicines (Mahesh et al., 2012). In the Indian system of medicine, it is commonly called '*Punarnava*' (Mahesh et al., 2012). *Boerhavia* belongs to the family Nyctaginacee. It is an herbaceous perennial weed (Mahesh et al., 2012). It possesses a greenish or purple cylindrical stem and mostly common stalk with branches, and it will grow to a height of more than 1 meter. Leaves are slender and arranged oppositely in unequal pairs; the leaves framework is about rounded apex or sometimes pointed slightly. The inflorescence is axillary and terminal umbel. Flowers' color varies from light pink to dark pink, bearing the size of 2.5 to 3 mm, possessing both males and females in the same flower. *B. diffusa* fruits come under achene type; the fruit's shape and size vary from ovate, pubescent, and possessing five ribbed. *B. diffusa* has several medicinal properties; it has several bioactive compounds which will cure

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or treat diseases like ascites, anasarca, and jaundice (Devaki et al., 2005). In addition, it cures spleen enlargement, coronary heart diseases, bacterial infection, diabetes, elephantiasis even infertility and menstrual pain (Apu et al., 2012). According to Mishra et al. (2014), this plant extract is used along with some formulations to treat rheumatism, nephrological, anemia, and gynecological disorders.

63.2 BIOACTIVES

The *B. diffusa* contains many chemical and bioactive compounds, such as steroids, alkaloids, flavonoids, lignins, lipids, carbohydrates, and proteins. B. *diffusa* extract has an excellent nutritional value, 100 g of extract has 44 mg of Vitamin C, 22 mg of Vitamin B2. It has mineral contents viz., sodium, iodine, and magnesium (Riaz et al., 2014). The major compounds in *B. diffusa* are hypoxanthine, L-arabinofuranoside, ursolic acid, lunamarine, palmitic acid, beta-ecdysone, Glutamic acid, Stigmasterol. The entire plant is filled with biochemical constituents like 'punaranavine' ($C_{17}H_{22}N_2O$), beta-sitosterol, liriodendron, and some salts like potassium nitrate (16%); it also has sequence of boeravinones, namely boeravinones A, boeravinones B, boeravinones C, boeravinones D, boeravinones E, boeravinones F, respectively (Ghosh, 2018). Besides being bioactive, *B. diffusa* also contains 15 amino acids (Chaudhary and Dantu, 2011). Leaves have chemicals like flavonoid glycoside class which includes Eupalitin 3-O-galactosyl (1→2)glucoside, 3,4-dihydroxy-5-methoxycinnamoyl rhamnoside, eupalitin-3-O-β-D-galactopyranoside, quercetin 3-O-rhamnosyl (1→6) galactoside (quercetin 3-O-robinobioside) and kaempferol 3-O-robinobioside. Chloroform extract (CE) and ME from leaves of *B. diffusa* contain caffeic acid, ferulic acid, D-pinitol, which have a wound healing potential (Juneja et al., 2020). Roots contain phenolic acid (trans-caftaric acid) and some roteniods, lignin, xanthone, and sterol (Mishra et al., 2014). C-methyl flavone is extracted from the roots of *B. diffusa.* Seeds of *B. diffusa* contain fatty acids, allantoin, and *B. diffusa* green stock has been analyzed to contain boerhavin and boerhavic acid (Mahesh et al., 2012). The important compounds present in *B. diffusa* are represented in Figure 63.1.

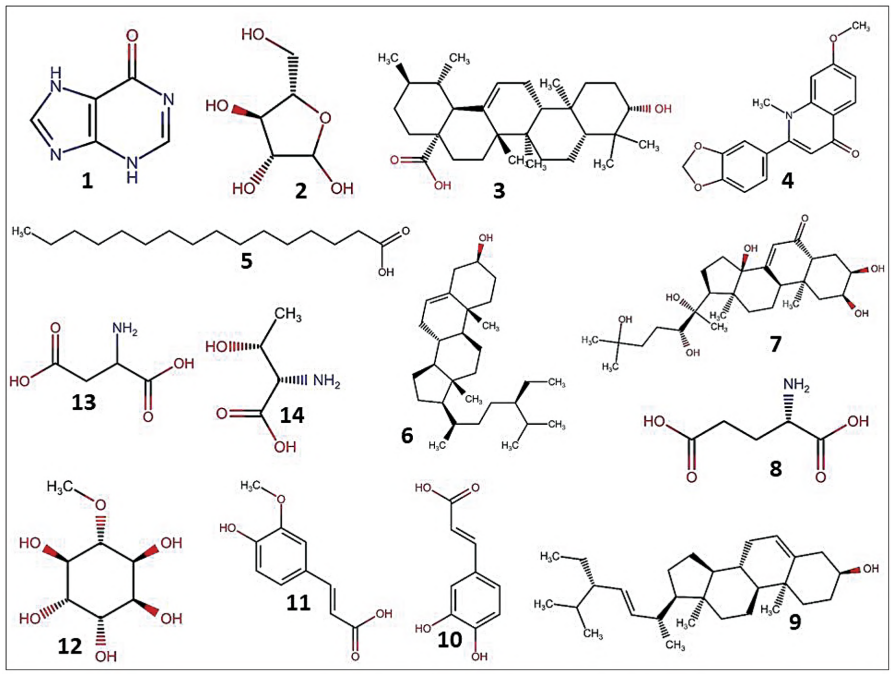


FIGURE 63.1 Chemical structures of *Boerhavia diffusa*. (1) Hypoxanthine; (2) L-arabinofuranoside; (3) ursolic acid; (4) lunamarine; (5) palmitic acid; (6) beta-sitosterol; (7) beta-ecdysone; (8) glutamic acid; (9) stigmasterol; (10) caffeic acid; (11) ferulic acid; (12) D-pinitol; (13) aspartic acid; and (14) threonine.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

63.3 PHARMACOLOGY

63.3.1 ANTIDIABETIC ACTIVITY

Diabetes mellitus (DM) is a significant problem affecting humanity in every nook and corner of the world. For control, several methods are undertaken by researchers. The extracts of *B. diffusa* plant show a positive effect on controlling DM by exhibiting antidiabetic activity (Kumar et al., 2018). When *B. diffusa* leaves extract was given to streptozotocin (STZ)-induced hyperglycemic rats, they showed a decrease in blood glucose contents. *B. diffusa* extracts were known to increase the rejuvenation of β cells in the pancreas (Kumar et al., 2018; Kaur et al., 2020). According to Ghosh (2018), destruction of beta cells occurs due to exposure to alloxan, and the regeneration of β cells is due to the effects of the drug treatment in alloxan-injected

guinea pigs. In comparison with Glibenclamide (25 micrograms/kg) and *B. diffusa* extracts (200 mg/kg), both reduce the blood sugar level by 59% and 38.65%, respectively, which is almost a comparable value (Mishra et al., 2014). So, *B. diffusa* extracts naturally possess antidiabetic activities.

63.3.2 ANTIBACTERIAL ACTIVITY

The *B. diffusa* ethanolic leaf extract has antibacterial activity countering several bacterial groups that threaten human beings like *Neisseria gonorrhoeae, Streptococcus* spp., *Shigella dysenteriae*, *Clostridium tetani* and *Salmonella typhimurium* (Mishra et al., 2014). *B. diffusa* leaves extract showed an inhibitory response for gram-positive and gram-negative bacteria (Kumar et al., 2018). *B. diffusa* leaves have the highest susceptible activity on *Escherichia coli* and *Streptococcus aureus* and are least susceptible to *Pseudomonas aeruginosa*. The extracts have shown their success in treating tuberculosis; the affected patients are treated with *B. diffusa* extracts showing 80% recovery of cough and 88% recovery of higher body temperature. They can recover quickly within six weeks compared to standard control (Mishra et al., 2014). The antibacterial activity of *B. diffusa,* determined by disc diffusion assay where the *E. coli* spread on nutrient agar medium. The leaves extract, administered into the medium and then incubated at 37°C. overnight. The zone of inhibition determines the effectiveness. The methanolic leaf extract, acetone, and hydro-extract *B. diffusa* were studied. Among them, the methanolic extract showed more significant inhibition of 5 cm for *E. coli*, and the remaining extract showed inhibition zones between 3 cm and 4 cm (Gujar and Billore, 2017).

63.3.3 ANTI-ULCER ACTIVITY

Gastric ulcer occurs due to the imbalance between the gastroduodenal defense substance and mucosa damaging substance, which causes damage or wounds on the intestine (Kaur, 2019). The ethanol extract of *B. diffusa* contains antacid properties, giving fast relief for gastric ulcers. The ulcer index rate was reduced when the patients are administered with extracts (Kumar et al., 2018). When experimentally analyzing the anti-ulcer activity, the pyloric ligation ulcer model was considered. The male albino rats (150–200 g) of different groups, where one group is administered with basic saline of (2 ml/kg), the next one with *B. diffusa* extract of (5 ml/kg) and another group with

standard drug ranitidine (20 mg/kg) for four consecutive days. After four days, the rats were assessed by measuring gastric contents and the nature of mucosal membranes. The overall result shows that *B. diffusa* extracts can control ulcers (anti-ulcer activity), but it was not to that extent of ranitidine (Gharate and Kasture, 2013).

63.3.4 IMMUNOMODULATORY ACTIVITY

The extracts have a good value of immunomodulatory, which shows a reduced mortality rate when the rat was induced by *Escherichia coli*-induced abdominal sepsis. It also decreases the hypersensitive reaction in animals. *B. diffusa* root extracts were used to test albino mice for antistress and adaptability activity; they show excellent stress resistance and immunomodulatory activity. It also triggers the lymphocytes and accessory cells and increases the delayed-type hypersensitive (DTH) response to sheep red blood cells (SRBC) in mice (Mishra et al., 2014). In an experiment, *B. diffusa* plant extract has an alkaloid 'punaranavine' was administered to BALB mice (20–25 g) of 4–6 weeks old. It is divided into different groups. One is fed with normal saline, which acts as a control, and another with punaranavine extracted from *B. diffusa*. The weight of each organ, WBC, and hemoglobin count were measured before plant extract administration. The extract is given to rats for 30 days consecutively. The output shows an increase in the weight of body organs (like the spleen, thymus). The WBC count is doubled compared to control, but the hemoglobin count remains the same; no significant change is noticed. But the negative side is that plague cell count is increased (Manu and Kuttan, 2009).

63.3.5 CARDIOPROTECTIVE ACTIVITY

The plant *B. diffusa* was collected, dried, and made into powder. It was extracted using different solvents (chloroform, ethyl acetate (EAE), petroleum ether), and albino rats were chosen for the study. The rat models were allocated into different groups. The rats were induced with a doxorubicin drug which causes myocardial damage. One group is administered with normal saline, another one with standard drug Vit-E, and the remaining groups with different forms of *B. diffusa* extracts continued for two weeks consecutively. After the experiment, the result showed that doxorubicin-treated rats have increased LDH, CK-MB, and cTn-I diagnostic markers,

indicating myocardial damage. However, the *B. diffusa* extracts and Vit-E-treated rats showed a decreased level of LDH, CK-MB, which indicates *B. diffusa* extracts are not harmful to the heart; they can restore myocardial damage (Nimbal and Koti, 2017).

63.3.6 HEPATOPROTECTIVE ACTIVITY

The liver is the body's first defense mechanism, so protecting it from external chemicals is very important (Kumar et al., 2018). Ethanolic exctracts of plant roots, stems, and leaves have a hepatoprotective action against acetaminophen-induced hepatotoxicity in rats and due to carbon tetrachloride (CCl_4) exposure (Kaur et al., 2020). For hepatoprotective activity, the extracts collected from roots should depend on seasons. The evidence showed that the aqueous form of the extract is more effective than the powder form (Ghosh, 2018).

63.3.7 ANTITUMOR ACTIVITY

An investigation was done to evaluate the antiestrogenic and antiproliferative characteristics of methanolic leaf extract of *B. diffusa* (BME) in breast cancer cell lines (MCF-7). The efficient concentration limit of BME towards cell sustainability was examined utilizing MTT assay. The antagonistic binding of BME to the estrogen receptor (ER) was verified by carrying out a Hydroxylapatite assay (HAP). The influence of BME on the expression of a selected estrogen-responsive gene *pS2* was investigated by RT-PCR. The capacity of BME to modify the cell cycle stages and distributions were investigated using FACS analysis. Different concentrations of BME were used for treatment (20–320 µg/mL), which resulted in an average to potent growth repression in MCF-7 cell lines. BME competed with [3H]-estradiol for coupling to ER with an IC_{50} value of 320 ± 25 µg/mL. RT-PCR study unveiled that BME decreased the mRNA expression of *pS2*, symbolizing the antiestrogenic effect of BME. BME treatment for two days followed a notable improvement in the number of MCF-7 cells in the G0–G1 fraction from 69% to 76%, with a correlative drop of cells in all other phases registering cell cycle interruption at the G_0–G_1 phase. The outcomes confirm that *B. diffusa* holds antiestrogenic and antiproliferative characteristics and hint that it may have healing potential in estrogen-dependent breast cancers (Sreeja and Sreeja, 2009). Experiments were conducted by orally feeding of

B. diffusa extracts to the affected rats for 14 days with dosage level of 125 and 250 mg/kg based on the bodyweight of rats, it exhibits antitumor activity by preventing the formation of active carcinogens and detoxification process (Mahesh et al., 2012). Moreover, based on the study, *B. diffusa* extracts has antitumor activity, determined by the MIT assay method. The standard drug used was tamoxifen (100 μmg/ml). After several steps, the inhibition by drugs was assessed and compared. *B. diffusa* extract (200 μmg/ml) showed significant inhibition (52.86%), while tamoxifen showed 76.6% response. Thus, *B. diffusa* extracts have antitumor activity, and its efficiency value is moderately comparable to tamoxifen (Muthulingam and Chaithanya, 2018).

63.3.8 ANTI-INFLAMMATORY ACTIVITY

The bioactive compounds present in the extract of *B. diffusa* were tested for anti-inflammation properties, namely kaempferol, liriodendron, quercetin, respectively (Mishra et al., 2014). Male rats were injected with lambda–carrageenan and saline, which induces inflammation in rats and causes edema within 3–4 hrs. Then, the rats were administered with *B. diffusa* extracts (5 ml/kg) and (2.5 ml/kg) on two different doses and Ibuprofen, a standard drug (40 mg/kg), were used. The antinociceptive compounds of *B. diffusa* present in plant extract show that it decreases rat paw edema and inhibits abdominal pain in mice. The final results show *B. diffusa* extract cures inflammation and pain very effectively on comparing with Ibuprofen. BD extracts of 5 ml/kg dosage work more effectively than 2.5 ml/kg (Gharate and Kasture, 2013).

63.3.9 ANTIOXIDANT ACTIVITY

B. diffusa aqueous extract of leaves has more potent antioxidant properties than roots. The antioxidant property is fundamental because it mitigates free radicals; it is the primary cause of severe diseases like cancer, heart disease, and stroke. The leaf ethanolic extract of *B. diffusa* has better antioxidative properties than the methanolic leaf extract of *B. diffusa*. Moreover, intake of *B. diffusa* leaf extracts (200 mg/kg) for 28 days showed a drop in hydroperoxides, thiobarbituric acid reactive substance, and a significant increase in reduced glutathione (GSH) peroxidase and GSH S-transferase in liver and kidney of alloxan-induced diabetic rats (Kumar et al., 2018).

Various portions of *B. diffusa* methanolic extract of root were analyzed for flavonoids, phenolics, nitric oxide (NO), and DPPH free radical scavenging

actions. The entire phenolic content was estimated in various fractions using various solvents like *n*-butanol, ethanol, diethyl ether, chloroform, and EAE to find their antioxidant activities. The phenolic content was more in the ethanolic fraction that was significantly equivalent with the ascorbic acid standard. The ethanolic fraction has the highest flavonoid content (41.9 ± 3.9 µg/mL) followed by *n*-butanol (31.6 ± 1.7 µg/mL), then EAE (29.6 ± 2.8 µg/mL) and scarce in chloroform fraction (16.91 ± 2.7 µg/mL). The ethanolic fraction of *B. diffusa* exhibited a significantly higher DPPH ROS mitigating activity (101.2 ± 3.7) than the other fractions of the same extract utilizing various solvent phases. Further, the NO scavenging action of the ethanolic fraction was highest (82.3 ± 2.8) among all fractions. The ethanolic fraction revealed increased ABTS cation mitigating activity (81.7 ± 2.7 mg/mL), while the chloroform fraction showed reduced ABTS radical cation mitigating activity (29.5 ± 2.7 mg/mL) (Khalid et al., 2020).

63.3.10 ANTI-HELMINTHIC ACTIVITY

Helminths are parasitic worms that obtain nutrients and shelter by making humans sick. The root extract of *B. diffusa* on oral intake kills helminths in children and adults (Kumar et al., 2018). The *B. diffusa* root extract was tested against Earthworm (*Pheretima posthuma*) model collected from the humid soil model. It is similar to helminths present in human beings. *B. diffusa* contains flavonoids, saponins, and phenolic compounds that possess anthelmintic activity. These extracts were administered in 3 doses (25, 50, 100 mg/ml), and for comparison, metronidazole, a standard drug, was used, and time taken for paralysis and death is calculated for analysis. Earthworms were put into the petri dishes and tested for their mortality, along with *B. diffusa* extract; the worms got paralyzed and died. The result indicated that *B. diffusa* extracts show a comparable value of metronidazole with a similar timing for paralysis and minor variation of time for death (Rajagopal, 2013). Albendazole is a standard drug instead of metronidazole in another study. Various *B. diffusa* solvent extracts were used *viz.,* EAE, methanol, and hexane. EAE conferred an excellent result for killing the helminth worms (Gautam et al., 2016).

63.3.11 ANTI-ARTHRITIC ACTIVITY

Arthritis is deadly to aging and causes pain in joints and swelling, and the most common types of this disease are osteoarthritis and rheumatoid

arthritis. According to Dapurkar et al. (2013), Freund's adjunct-induced arthritis (CFA) model was used to determine the anti-arthritic activity of *B. diffusa.* For the test, Wistar albino rats (150–200 g) were used. The extract of *B. diffusa* was dried and powdered and kept ready for administration. Arthritis was artificially induced into rats by injecting 0.1 ml of killed *Mycobacterium tuberculosis* which is homogenized in liquid paraffin. The albino rats were divided into five groups; one was fed by normal saline, another one with indomethacin (standard drug), and the other two with *Boerhavia diffusa* extract at different dosage levels 500 ml/kg and 1,000 ml/kg. After 21 days of treatment, *B. diffusa* leaves extract of 1,000 ml/kg showed a higher efficiency of 81.58%, used for arthritis treatment.

63.3.12 NON-TERATOGENIC ACTIVITY

Teratogen is a compound that causes disturbance to the embryo and fetus. When the pregnant albino female rats were administered, 250 mg/kg of *B. diffusa* extract showed promising results. It does not affect the embryo, and even the young ones remain as usual without any defects. So, it clearly shows that *B. diffusa* has a non-teratogenic activity (Nayak and Thirunavokkarasu, 2016).

63.3.13 EFFECT ON MALE REPRODUCTIVE ORGAN

B. diffusa extract has some adverse effects on the male reproductive organ. The male Wistar rats were selected for the study, and the *B. diffusa* leaves extract was administered. For the experiment, the rats were divided into different groups. One group is fed orally with normal distilled water; the remaining groups with *B. diffusa* extracts of doses (50, 100, 150 mg/kg) were administered to rats for 60 days consecutively. There was no notable variation in the serum testosterone level within *B. diffusa* leaf extract administered to rats and control. However, the weights of the seminal vesicles, epididymis, and testes were significantly reduced in dosed rats related to the control. Sperm count and sperm motility deteriorated significantly in the administered rats correlated with the control. Besides, the sperm dead-live ratio lowered notably in rat models administered with 100 and 150 mg/kg of the *B. diffusa* leaf extract correlated with the control. In histopathological studies, the testes of *B. diffusa* leaf extract-dosed rats exhibited spermiostasis with degeneration of germinal epithelia. This result hints that hydro-extract of

B. diffusa exhibited unfavorable consequences in the testicular morphology and semen of the rats (Adenubi et al., 2010).

Benign prostatic hyperplasia (BPH) is prevalent among older men. Concerned men have augmented prostate glands and encounter difficulties while urinating (Lee, 2008). The study was carried out by Vyas et al. (2013) to study the effect of hydroalcoholic extracts prepared from roots of *B. diffusa* on BPH in rats. Testosterone diffused in *Arachis* oil was applied subcutaneously in Wistar male rats for 28 days to induce BPH. The rats exhibited a notable increase in prostate mass when correlated with negative control. However, therapy with *B. diffusa* extract significantly lowered the prostate mass. *B. diffusa* extract attenuated the contractile response of the vas deferens and the prostate gland. Histo-architecture of the prostate gland also showed changes in rats treated with both *B. diffusa* and testosterone. It was inferred that the anti-inflammatory and antiproliferative properties of bioactive compounds in *B. diffusa* extracts might have comforted the smooth muscles of the prostate, and relieved the urinary symptoms of BPH disease.

63.3.14 ANTI-OBESITY ACTIVITY

For this study, *B. diffusa* roots, the ethanolic leaf extract was taken and administered to 2–4 months-old rats weighing 190–210 g. The rats were divided into four groups; group I is fed orally with normal saline, group II is fed with a high-fat diet (HFD) (20 gm/day/rat), group III is administered with a high-fat diet + *B. diffusa* extract (400 mg/kg), group 4 is with high-fat diet + Orlistat (standard drug) (10 mg/kg). This procedure is continued for 28 days. The final output shows that *B. diffusa* extract and the standard drug have reduced the increasing percentage of weight compared to the remaining groups, which shows that *B. diffusa* extract has the potential antiobesity activity. However, its efficiency is lesser than standard drugs (Orlistat) (Singh et al., 2015).

63.3.15 ANTIPYRETIC ACTIVITY

Determination of the antipyretic activity of *B. diffusa* was done in albino rats. For the experiments, the rats were divided into different groups. One group was used as a vehicle (0.1 ml/kg), another group with *B. diffusa* extract (5 ml/kg), and another one with Ibuprofen, a standard drug (40 mg/kg). Fever was induced in the rats by injecting Brewer's yeast in saline (1 ml/100 g.s.c)

in the neck region. Brewer's yeast in saline induces fever and causes sickness in rats. After 18 hrs., the rectal temperature increases gradually (above 2C than the average temperature). After treatment, the temperature was measured every two hours. The final result showed a decrease in temperature with *B. diffusa* extracts and Ibuprofen, which indicates that *B. diffusa* extract has an antipyretic activity (Gharate and Kasture, 2013).

KEYWORDS

- **anti-helminthic**
- **antitumor activity**
- ***Boerhavia diffusa***
- **estrogen receptor**
- **high-fat diet**
- **punarnavine**

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CHAPTER 64

A Brief Review on Bioactives and Pharmacology of Flame of the Forest [*Butea monosperma* (Lam.) Kuntze]

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64.1 INTRODUCTION

Butea monosperma (Lam.) Kuntze (synon. *Butea frondosa* Roxb. ex Willd.) is native to the sub-tropical and tropical parts of the Indian subcontinent as well as southeast Asia. It belongs to the family Fabaceae. It is commonly identified as 'Flame of the Forest' and Bastard teak in English; *Kimsuka*, *Raktapuspaka* in Sanskrit; *Palash* in Bengali; Punjabi: *Palas, Dhak, Tesu*; Tamil: *Parasu, Paras*; Hindi: *Dhak, Tesu*; Oriya: *Porasu*; Gujarati: *Kesudo*; Kannada: *Muttug*, *Muttala*; Urdu: Dhak, *Palaspada;* Telugu: *Moduga*; Marathi: *Palas* (Kirtikar and Basu, 1935; Patil et al., 2006). It grows all over the Indian states, but notably in Indo-Gangetic plains. This tree is considered to be a sort of Agnidev, also called the 'God of fire.' The tree's height may reach up to 50 ft and grows a cluster of flowers. The tree drops its foliage during flower blossom; this happens within the first three months of the year (Kirtikar and Basu, 1935; Kapoor, 2005). This tree holds a significant place due to its therapeutic and other diverse uses of great commercial importance. Its bark and young root fibers are obtained for producing cords or ropes. The bark powder is used commonly to paralyze fishes. Leaves of this tree are utilized to create cups, platters, bowls, beedi wrappers, and in the making of Ghongda, which shields buffaloes, elephants, and other cattle. The foliage of

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the tree is an excellent feed for livestock. Tribals' use the fruits and flowers of this tree as vegetables. The seeds are used in Unani and ayurvedic medicine, which can treat various disorders. Orange and red dyes are obtained from this tree by boiling its flowers in water, and then they are used for coloring and in the preparation of antiseptic creams. Flowers are also offered as a substitute for blood in sacrifices and rites for Kali, the Hindu Goddess (Ambasta, 1986).

Flowers of *Butea monosperma* are widely used in treating various disorders like diarrhea, viral hepatitis, hepatic disorder, depurative, and tonic. *Butea monosperma* is also used in the form of astringent, tonic, diuretic, and also as an aphrodisiac (Nadkarni, 2002). Flavanoids are extracted from its flowers. The contents present in the flowers include isobutrin, butrin, butein, isocoreopsin, plastron, and coreopsin. From the stem, euphane triterpenoid 3a-hydroxyeuph-25-ene and the alcohol 2,14-dihydroxy 11,12-dimethyl-8-oxo-octadec-11-enylcyclohexane has been isolated (Mishra et al., 2000). Mediacarpin from *B. monosperma* has antifungal activity. From the pods of *B. monosperma*, Imide palasimide has also been isolated. The traditional medication system claims that the plant may be a rejuvenator and categorized as a multipurpose tree with extensive therapeutic and commercial usefulness.

64.2 BIOACTIVES

The flowers of *Butea monosperma* possess glucosides and flavanoids. The main phytoconstituents of its flowers include isobutrin, butein and butrin. Coreopsin, palasitrin, isobutyine, isocoreopsin (butin 7-glucoside), chalcones, aurones, triterpene steroids, and monospermoside are the other phytoconstituents present within the flower (Sutariya and Saraf, 2015; Mishra et al., 2000). Roots are known to have glucosides, glycine, glucose, and other aromatic compounds (Parashar et al., 2011). Phyto-constituents like palmitic acid, lignoceric acids, aspartic acid, myricyl alcohol, arachidic, phenylalanine, stearic, histidine, fructose, and alanine are present in flowers (Sindhia and Bairwa, 2010). The seed oil contains lipolytic enzymes, polypeptidase, plant proteinase, and proteolytic enzymes. A potential antiviral flavone glycoside was isolated from the seeds of *Butea monosperma* was later identified as 5,2'-dihydroxy-3,6,7'- trimethoxyflavone-5-O-β-D-xylopyranosyl-(1→4)-O-β-D-glucopyranoside. The two flavonoids which are present are isobutrin and butrin. A flavone glycoside compound was isolated from the methanol soluble fraction of the flowers of *Butea monosperma* which

was later identified as 5,7-dihydroxy-3,6,4′-trimethoxyflavone-7-O-α-L-xylopyranosyl-(1 → 3)-O-α-L-arabinopyranosyl-(1 → 4)-O-β-D-galactopyranoside have shown to possess the antimicrobial activity against various fungal species. The number of flavonoids which are present in *B. monosperma* includes, coreopsin, palsitrin, monospermoside, isomonospermoside, butin, sulfurein, and butein (Sindhia and Bairwa, 2010).

The flavones called quercetin had been isolated from the stem bark of the plant, *Butea monosperma*. Two isoflavonoids that were isolated has been identified as 5-methoxygenistein and prunetin (Mishra et al., 2012). The bark contains several tannins like gallic acid, butolic acid, allophonic acid, lupenone, mirestrol, palasimide, shelloic acid, kino-tannic acid, lupeol, mediacarpin, histidine, and pyrocatechin (Nadkarni, 1976). The leaves contain glucosides; 3-alphahydroxyeuph-25-enylheptacosanoate, 3,9-dimethoxypterocapan, linoleic acid, and palmitic lignoceric acid (Mishra et al., 2000). The gum of this plant has tannins, mucilaginous material, and pyrocatechin (Kritikar et al., 1918). The stem of *Butea monosperma* has two aliphatic compounds, which are identified as 3-hydroxyl-25-ene and 2,14-dihydroxy-11, 12-dimethyl-8-oxo-octadec-11-enylcyclohexane. Nanocosanoic acid has also been isolated from the stem of this plant. The seed coat of *B. monosperma* consists of two aliphatic long-chain hydroxyl acids and a derivative of hydrazine which were isolated and identified as 15-pentacosanoic hydroxyl acid and 1-carbomethoxy-2-carbomethydrazine. From the seeds, aliphatic compounds were isolated and identified as 2-hydroxylmethyl allophonic acids (Mishra et al., 2012). The chemical structures of a few important compounds in *Butea monosperma* are represented in Figure 64.1.

64.3 PHARMACOLOGY

64.3.1 ANTI-INFLAMMATORY ACTIVITY

The leaves of *B. monosperma* display anti-inflammatory activity. This methanolic infusion of *B. monosperma* is assessed by the carrageenan-provoked paw edema and cotton bead-induced non-benign tumors. In carrageenin-induced paw edema at 600 and 800 mg/kg doses of the active ingredient, restraint of paw edema was observed to the tune of 26% and 35%, respectively, and inhibition of cotton pellet-induced tumor inhibition by 22% and 28%, respectively (Sindhia and Bairwa, 2010). *In-vitro* inflammatory

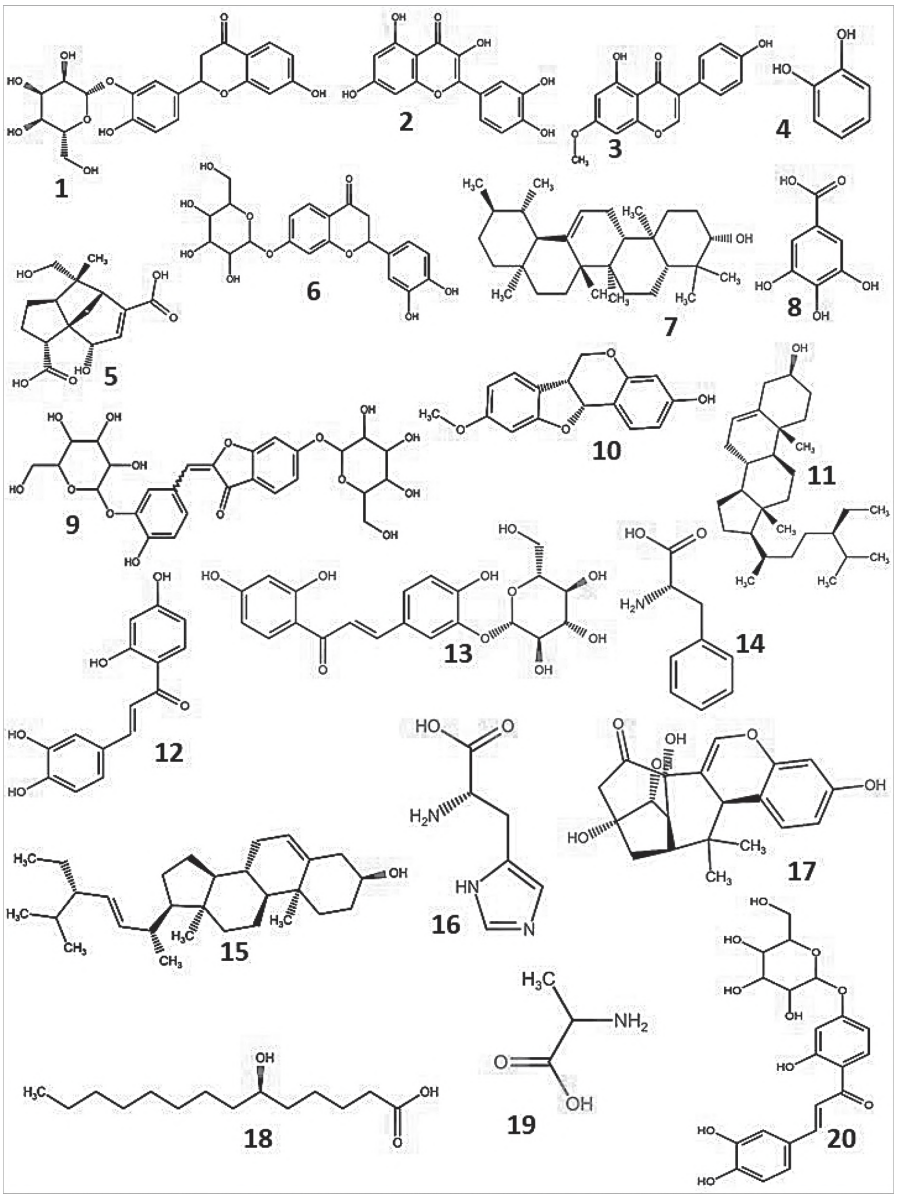


FIGURE 64.1 Chemical structures of a few important compounds in *Butea monosperma. (1) Isomonospermoside; (2) quercetin; (3) prunetin; (4) pyrocatechin; (5) shellolic acid; (6) isocoreopsin; (7)* α-amyrin*;* (8) gallic acid*;* (9) palasitrin*;* (10) medicarpin*;* (11) beta sitosterol*;* (12) butein*;* (13) monospermoside*;* (14) phenylalanine*;* (15) stigmasterol*;* (16) histidine*;* (17) mirsesterol*;* (18) butolic acid*;* (19) alanine*;* and (20) coreopsin.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

activity was assessed by the 'Human red blood cell membranes' stabilization process. Samples were prepared with the various extracts at a one milligram per milliliter dosage with 2% acacia extract, and Diclofenac suspension was used as the control. Chloroform and petroleum ether infusions of *B. monosperma* exhibit potent anti-inflammatory action, whereas ethanol, hexane, and ethyl acetate (EAE) exhibit average anti-inflammatory action (Mishra, 2016).

64.3.2 ANTI-DIABETIC ACTIVITY

Butea monosperma (flower) extracted significantly decreased blood glucose, and serum cholesterol and improved High-density lipid-cholesterol and antioxidant enzymes' activities (Somani et al., 2006; Sharma and Garg, 2009; Talubmook et al., 2014). The flower extracts exhibited lipid-lowering and antidiabetic activity (Parveen and Siddiqui, 2011). The *B. monosperma* flowers (n-butanol fraction) remarkably reduced dexamethasone-provoked hyperlipidemia and hyperglycemia (Jamkhande et al., 2010). *B. monosperma* revealed significant antidiabetic action with various *in-vitro* procedures, glucose adsorption, diffusion, glucose transport across yeast cells, amylolysis kinetics, and enteric enzymes activity over baker's yeast (Harish et al., 2014).

The hydro-ethanolic bark extract of *B. monosperma* (Yadav et al., 2012; Divya and Mini, 2014) and the seeds conferred lipid-lowering and antidiabetic activity (Bavarva and Narasimhacharya, 2008). Besides, stigmasterol separated *B. monosperma* (bark) and decreased serum glucose, triiodothyronine, hepatic glucose-6-phosphate, and thyroxin levels with a synergistic boost in insulin (Panda et al., 2009). The oral administration of *B. monosperma* at various doses lessened urine sugar, blood glucose, LDL cholesterol, and total lipids significantly. It enhanced HDL cholesterol in both standard and diabetic cases (Akhtar et al., 2010).

64.3.3 ANTHELMINTIC ACTIVITY

B. monosperma seeds are utilized in the Ayurvedic practice in the application of anthelmintic medication. The powdered seeds conferred a concentration-dependent (three grams per kilogram) and a time-dependent anthelmintic action in treated animals (sheep). The anthelmintic activity of *Butea monosperma* has been recorded upon earthworms, *Ascaridia galli, Ascaris*

lumbricoides, Toxocara canis, Diphylidium caninum, Taenia solium, and various pinworms (Sindhia and Bairwa, 2010).

A compound called palasonin, which was obtained from the seeds of *Butea monosperma* has been proved to have antihelmintic properties. These seeds were administered as crude powder at the doses of 1, 2, and 3 g/kg to sheep naturally infected with a mixed species of gastro-intestinal nematodes exhibited a dose and time-dependent anthelmintic effect (Iqbal et al., 2006). The maximum reduction of 78.4% in eggs per gram of feces has been recorded on the 10th day after the treatment with 3 g/kg. The standard anthelmintic agent called Levamisole (7.5 mg/kg), exhibited 99.1% reduction in eggs per gram. Methanolic extract of *Butea monosperma* seeds showed significant anthelmintic activity *in-vitro* (Mishra et al., 2012).

64.3.4 ANTI-DIARRHEAL ACTIVITY

Butea monosperma (bark) EE has been documented to restrain castor oil-provoked diarrhea, and PGE2 provoked fluid accumulation in the small intestine. Gastrointestinal motility decreased after the charcoal feed treatment (Gunakkunru et al., 2005). In cases of chronic diarrhea, *B. monosperma* gum has also been a potent astringent and decreases the bilirubin content (Mishra et al., 2012).

64.3.5 ANTI-CONVULSIVE ACTIVITY

Triterpene is the causal agent for the anti-convulsive activity in *B. monosperma*. This acetone-dispersible portion of the flower extract of petroleum ether of *B. monosperma* displayed anti-convulsant action (Kasture et al., 2000). Moreover, investigations unveiled that the triterpenes isolated from the n-hexane: EAE portion of the flowers have anti-convulsant action in pentylenetetrazol-provoked convulsions (Kasture et al., 2002). The leaf and bark extract of *B. monosperma* displayed an anti-convulsant outcome in the pentylenetetrazole and maximal electric impulse convulsion in animal models (Sangale et al., 2015). The *B. monosperma* fractions raised gamma-aminobutyric acid (GABA) and serotonin in the brain. Moreover, it defended animal models from the maximum electroshock, lithium-pilocarpine-induced, and electrically induced-pentylenetetrazole convulsions but missed to guard the animals against strychnine-provoked seizures (Sindhia and Bairwa, 2010).

64.3.6 WOUND HEALING ACTIVITY

The *B. monosperma* bark (hydro-ethanolic) extracts possess wound-healing properties in experimental animals (Gavimath et al., 2009); flavonoid fraction of *B. monosperma* bark exhibited wound-healing characteristics (Muralidhar et al., 2013). The acetone portion of EE of *B. monosperma* (bark) revealed the notable wound healing action, which was apparent by the wound compression, improvement in collagen deposition, and enhanced percentage of decline in the time of epithelialization (Muralidhar et al., 2011). As evidenced by the granulation tissues ' increase in protein, DNA, and collagen content, *B. monosperma* hastened wound healing by improving collagen organization and cellular propagation at the wound position (Sumitra et al., 2005).

64.3.7 ANTI-MICROBIAL ACTIVITY

The hydroalcoholic infusion (flowers) of *B. monosperma* has displayed antibacterial action upon pathogenic bacteria viz., *Escherichia coli* (Sharma et al., 2000). Likewise, the *B. monosperma* hydro-ethanol mixture has displayed notable antibacterial action towards many strains of bacteria (Sahu and Padhy, 2013). Bioactive flavonoids butein, monospermoside, isoliquiritigenin, dihydro chalcone and dihydro monospermoside from *Butea monosperma* flowers show anti-mycobacterial properties (Chokchaisiri et al., 2009). Desiccated flowers and the seeds of *B. monosperma* (ethanolic infusions) have excellent anti-microbial action towards pure cultures of *Salmonella typhi, Escherichia coli, Salmonella paratyphi, Pseudomonas aeruginosa* and *Shigella flexneri* (Tambekar and Khante, 2010). The ethanol-hexane blend extract of *B. monosperma* holds anti-microbial action towards MDR bacteria, viz, *Pseudomonas aeruginosa, Bacillus cereus* and *Escherichia coli* (Lohitha et al., 2010).

64.3.8 ANTIESTROGENIC AND ANTI-FERTILITY ACTIVITY

Alcoholic flowers extracts of *B. monosperma* possess antiestrogenic and anti-fertility, anti-ovulatory, and anti-implantation actions. Butin has been identified as the active constituent in it. Butin, separated from *B. monosperma* flowers confers male and female contraceptive properties (Mishra et al., 2012). The *Butea monosperma* (bark) extract resulted in separation

and identification of three compounds: butea spermanol, butea spermin B and buteaspermin A accompanying an additional 19 recognized compounds (Sindhia and Bairwa, 2010).

64.3.9 HEMOGLOBIN AGGLUTINATING ACTIVITY

Butea monosperma seed extracts confer specific action upon the human erythrocytes; extracts possess a lectin known as *Butea monosperma* agglutinin (BMA); this lectin was verified to be effective for its agglutinating characteristics. This attribute was revealed exclusively by the seeds and not by other parts of *B. monosperma* extracts. Human blood group A-specific agglutinins has been confirmed in N-acetyl galactosamine/galactose binding lectins. Hemagglutination analysis proved that the N-acetyl galactosamine is the most potent inhibitor of agglutination (Sindhia and Bairwa, 2021).

64.3.10 ANTI-ASTHMATIC AND ANTI-FILARIAL ACTIVITY

The n-butanol portion of *B. monosperma* has restrained lipopolysaccharide (LPS) and induced an increase in the albumin levels, total protein (TP) and cell count in the bronchoalveolar fluids (Shirole et al., 2013). The aqueous infusion of the *B. monosperma* repressed the motility microfilariae of *Brugia malayi* significantly. This effect has been identified in a dose-dependent manner with IC_{50} value at 83 ng/ml (Tiwari et al., 2019).

KEYWORDS

- **anti-asthmatic activity**
- **anti-fertility**
- **anti-implantation actions**
- **aqueous infusion**
- ***Butea monosperma***
- **flame of the forest**
- **gamma-aminobutyric acid**

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CHAPTER 65

Pharmacological properties and Bioactive Principles of Tea [*Camellia sinensis* (L.) Kuntze]

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65.1 INTRODUCTION

Camellia sinensis is a native plant of China and Southeast Asia and belongs to the family of flowering plants called Theaceae. It is an evergreen shrub or small tree of 10–15 m in length. While cultivating, the length is reduced to 0.6–1.5 m. It has yellow to white flowers of 2.5–4 cm diameter with solitary or clusters holding 7–8 petals (Namita et al., 2012). Flowers have numerous stamens containing yellow anthers, which will produce brownish-red capsules. The economic part of the plant is its leaves. Leaves are coriaceous, alternate, lanceolate, serrate margin, and glabrous, with length from 5–30 cm and width of 4 cm. It can be grown in areas with a proper temperature, acidic soils, and highly humid environmental conditions (Mahmood et al., 2010). For harvesting, leaves should be young and light green, having some hairs on the underside. Mature leaves look green in color. Leaves are harvested at the stage of the first and second leaf stages manually. Twig tea is also made from *Camellia sinensis,* where twigs and stems are collected instead of leaves. Tea is one of the most used refreshments globally, and it has much therapeutic value.

In general, tea is categorized into six principal groups based on fermentation procedures. They are black tea (entirely fermented to the extent of 80–100%), dark tea (post-fermented to more than 100%), oolong tea (30–60%;

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semi-fermented), yellow or white tea (slightly fermented; 10–20%) and green tea (non-fermented) (Xu et al., 2018). The Common name of a plant varies from place to place. In India, it was known as Chhai, whereas in China, it was called Cha. In Russia, it is named Chai. At present, tea is cultivated in around 30 countries in the world. Tea is considered to be a medicinal plant in China and India. It is also used in Ayurveda, Unani, and Homoeopathy (Namita et al., 2012). Green tea comprises the highest intensity of antioxidants as it has various polyphenols. Medicinal properties are mainly because of its polyphenols, chemicals with antioxidant properties. Green tea extract is used as an effective treatment for acne as it helps to decrease hormonal activity. It prevents colon, pancreatic, and stomach cancers. It stimulates the body's immune system and protects it from diseases. It helps regulate body temperature, maintains blood sugar, promotes digestion, and helps to relieve stress (Chopade et al., 2008).

65.2 BIOACTIVES

There are around 4,000 bioactive compounds found in *Camellia sinensis*. Out of this, polyphenols occupy one-third of these compounds. Polyphenols include catechins which give significant health benefits to tea. Major catechins include epigallocatechin (EGC), epicatechin (EC), epigallocatechin gallate (EGCG) and epicatechin gallate (ECG). Among these, epigallocatechin-3-gallate is more active and abundant catechin in green tea (Namita et al., 2012). Tea catechins are tea flavanols that make 20–30% of the dry weight of green tea. Catechins are usually water-soluble compounds, colorless, impart a bitter astringency taste to the tea. Some direct or indirect modifications in catechins will cause changes in characteristics like tea color and aroma. Major tea flavonols include quercetin, myricetin, kaempferol which are also water-soluble (Mahmood et al., 2010). Green tea has alkaloids like caffeine, theobromine, theophylline. Other than this, tea leaves also contain purines, minerals, volatile oils, vitamins, polysaccharides, carbohydrates, amino acids, chlorophyll (Chopade et al., 2008). Studies show that in yellow tea, EGCG accounts for the most significant catechin proportion. On the other hand, catechin, and gallocatechin are in a minor proportion. In the fermentation process, oxidization of catechins leads to theaflavins production. These theaflavins are bright orange-red and necessary for beneficiary activities of all types of tea (Xu et al., 2018). Umami taste is given by Theanine and is also involved in biological activities like anti-tension and relaxation. In unfermented teas, Theanine is found to be more. The contents

in chemical compounds of tea are mainly dependent on tea types and tea grades. At the same time, the change in geographical factors results in the variation of polyphenols. Usually, polyphenols (flavan-3-ol) are rich in fresh leaves. Reports suggest that carbohydrate content present in tea is indicated by sucrose, fructose, lactose, and glucose, which have a value of 0.71%, 0.72%, 0.57%, and 0.68%, respectively, in 80% ethanol extract. During the brewing process, polysaccharides are the essential bioactive compounds extracted from tea leaves. In mature tea leaves, polysaccharides are present, which are surrounded by proteins and uronic acid. Also, fresh tea leaves have gallic acid, other phenolic acids, hydrolysable tannins. For example, hydroxycinnamic acids, quinic acid, hydroxybenzoic acids, caffeoylquinic acid, galloylquinic acid are present in tea leaves (Zhang et al., 2019). A few important compounds present in *Camellia sinensis* are given in Figure 65.1.

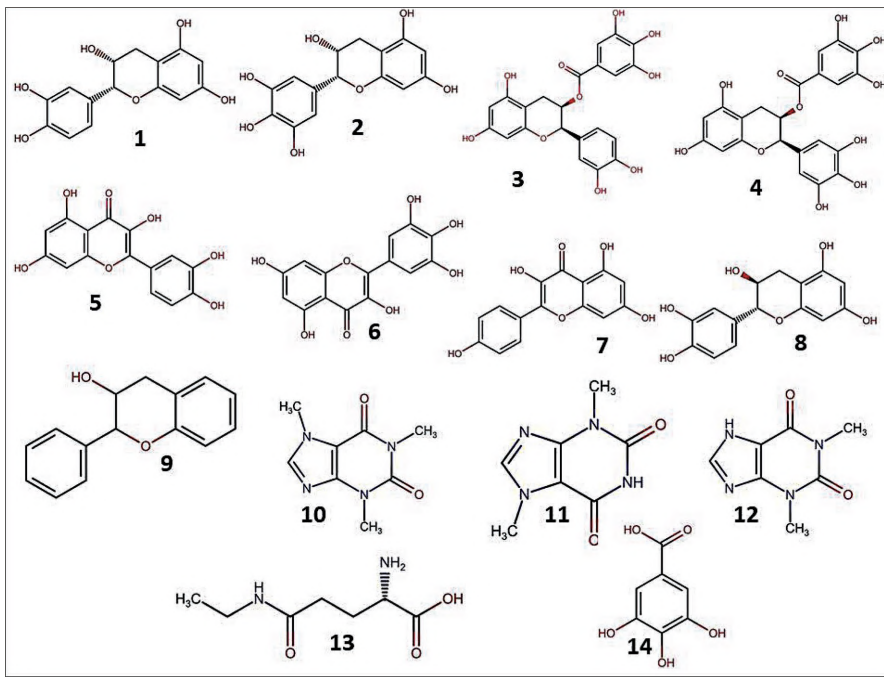


FIGURE 65.1 Chemical structures of the bioactive compounds in *Camellia sinensis*. Epicatechin (1); epigallocatechin (2); epicatechin gallate (3); epigallocatechin gallate (4); quercetin (5); myricetin (6); kaempferol (7); catechin (8); flavan-3-ol (9); caffeine (10); theobromine (11); theophylline (12); theanine (13); and gallic acid (14).

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

65.3 PHARMACOLOGICAL ACTIVITIES

65.3.1 ANTI-INFLAMMATORY ACTIVITY

Tea root extracts contain many compounds of therapeutic importance and pharmacological interest. In a study, rats were injected with Carrageenan (0.1 ml/100 g from 10 mg/ml solution) in the right-hand forefoot to induce edema. The weight of rats' left and right hind paw was measured after four hours by Plethysmometer and concluded that tree root extract (TRE) of tea inhibited this edema by 41%. Two cotton pellets were implanted into the groin region of the experimental rats subcutaneously to induce granuloma. A group of rats was given a dose of 10 mg/kg i.p of TRE for seven days consecutively, and weights were compared with control. Results proved that TRE suppressed the increase in dry weight by 44% compared to the increased weight of cotton pellet in the granuloma. Another test shows Freund's adjuvant (0.1 ml) was injected into the plantar pad of each rat. Rats were given a dose of 10 mg/kg of TRE for 21 days consecutively. The weights were measured before and after the administration of the adjuvant. The results indicated that TRE inhibits the development of arthritis by 49%, and secondary lesions were suppressed. It also proved that TRE shows 11% more suppressiveness in comparison to acetylsalicylic acid. Next, Arachidonic acid is injected into rats to induce paw edema. It proved that the dose of 10 mg/kg of TRE inhibited edema. Saponins are responsible for all the activities done by TRE. From TRE, two groups of saponins (TS-1, TS-2) were isolated, and it has been proved that they possess anti-inflammatory and antioxidant activities. TRE also plays a significant role in analgesic and antipyretic effects (Chattopadhyay et al., 2004).

65.3.2 ANTIDIABETIC ACTIVITY

In many antidiabetic therapies, molecular targets in signaling pathways are found to be the most successful. Research studies showed that active metabolites of tea have a beneficial effect against diabetes through various signaling pathways. Also, studies show that type II arabinogalactan separated from green tea increases insulin production (Sánchez et al., 2020). It also shows that without changing insulin levels, glucose levels can be reduced by green tea extract when supplying to the bloodstreams of diabetic mice. When supplying green tea extract to normal mice on a long-term basis, insulin

sensitivity is increased. Hyperglycemia, insulin resistance (IR), and other metabolic defects can be prevented by feeding green tea extract to diabetic rats (Namita et al., 2012). Combining 560 mg tea polyphenols two times/day for 20 weeks and 200 mg tea extract/day for 275 days to 500 days has proved to have an antioxidant effect of increased superoxide dismutase (SOD) activity and reduction in lipid peroxidation (LPO) (Sánchez et al., 2020).

Green tea polyphenols (GTPs) scavenge hydroxyl, superoxide radicals, and LPO with a concentration of 52.5, 136, 10 µg/ml. Glucose tolerance is increased in normal rats when supplying GTPs at a dose of 500 mg/kg b.w. In alloxan-induced diabetic rats, the serum glucose level is reduced by administering GTP at a dose of 100 mg/kg b.w. Alloxan produces elevated renal and hepatic enzymes. Serum levels were reduced by supplying GTP (Sabu et al., 2002). Catechins, caffeine, and theaflavins are attributes for the biological activities of the tea plant. In diabetic mice, tea is found to decrease blood glucose levels and, at the same time, protect pancreatic β cells. Studies show that the consumption of oolong tea (1,500 ml) for 1–2 weeks by type II diabetic patients decreases concentrations of plasma glucose and fructosamine. Polyphenols, particularly catechins, are responsible for improving glucose metabolism, in which EGCG is an active ingredient of diabetes mellitus (DM). Studies show that supplying EGCG at a dose of 2.5–10 g/kg of diet for about 5–10 weeks in diabetic fatty rat increases insulin secretion in the blood. EGCG also helps to increase the pancreatic effect and glucose-stimulated insulin secretion (Fu et al., 2017).

65.3.3 ANTI-CANCER ACTIVITY

Catechins present in green tea can inhibit tumor cell proliferation and promote the destruction of Leukemia cells. Both black tea and GTPs suppress cell growth and induce apoptosis of human cervical cancer cells. Studies show that green tea consumption protects against colorectal cancer. The studies conducted using animal models show that EGCG and green tea inhibits carcinogenesis at all stages, the process of angiogenesis, tumor metastasis, and invasion in animal models (Namita et al., 2012). Studies show that regular drinking of green tea will reduce the risk of breast cancer by up to 12%. A meta-analysis proved that increased green tea consumption was inversely proportional to the occurrence of breast cancer.

In contrast to this, epidemiological studies show that green tea was not related to decreasing the risk of these cancers. However, a Japanese study shows that people who regularly consume five and more green cups of tea

have a lower risk of liver cancer (Zhang et al., 2019). Some crucial mechanisms involved in carcinogenesis gets halted by green tea consumption. EGCG, present in green tea extract, blocks cell membrane receptors, inhibits cancer cell growth, lung metastasis and urokinase activity in animal models (Shirakami and Shimizu, 2018). Laboratory animal experiments have proved that polyphenols in green tea will inhibit the formation and involves in the destruction mechanism of heterocyclic amines. Recently, studies reported that polyphenols in green tea could prevent prostate cancer from preventing the spread by targeting molecular pathways, halting proliferation, the spread of tumor cells, and arresting the growth of tumor nurturing blood vessels (Johnson et al., 2010). It has also proved that EGCG inhibits the growth of breast cancer cell line Hs578t3 and estrogen-dependent, estrogen receptor (ER)-positive MCF-7 xenograft (Farabegoli et al., 2007). Recently, studies reported that theanine improves the anti-tumor activity of cancer drugs like doxorubicin, Adriamycin (ADP), pirarubicin, and idarubicin. Combining chemotherapeutic agents and theanine will sustain the high level of drug in tumor cells, slow down the growth, and increase tumor cells' death (Stearns and Wang, 2011). It will be more effective when theanine intake at 50–200 mg/day, i.e., 2–4 cups of green tea. A Japanese study resulted that consuming green tea will reduce the reoccurrence of stage I and II breast cancer but does not show any changes in advanced stages (Inoue et al., 2001). The extract of green tea will enhance the effect of anti-cancer agents like doxorubicin. Combing green tea with doxorubicin inhibited tumor growth in M5076 ovarian sarcoma cells but when doxorubicin alone supplied gives no effect against the same cell line (Cooper et al., 2005). *In vitro* studies using phytohemagglutinin mixed with green tea extract on lymphocytes decreases alloresponsiveness and has immunosuppressive effects (Wilasrusmee et al., 2002).

A study proved a reduced risk of stomach and esophageal cancers in China when a continuous intake of green tea of more than 1 g/month (Yu et al., 1995). In South America, another case study resulted in a lower incidence of esophageal cancer even if they consume more than 500 ml of tea per day (Madigan and Karhu, 2018). Epigallocatechin gallate (EGCG) stops cancer growth and developmental phases by protecting against free radical damage to DNA. Green tea reduces cancer metastasis, leading to a reduction in the expression of adhesion molecules and metalloproteinases (Koo and Cho, 2004). There are many bioactive compounds in herbal teas that help in reducing the risks of chronic diseases. A test was done on EGCG, quercetin, gallic acid, green tea, Ardisia tea, and mate tea. Results suggest that Ardisia

tea, mate tea, and green tea were cytotoxic to HepG2 cells showing that mate tea has dominant cytotoxicity (Bhatt et al., 2010).

65.3.4 ANTIMICROBIAL ACTIVITY

By using tea extracts, rotavirus, and enterovirus can be prevented in the kidney cells of monkeys (Mukoyama et al., 1991). Tea extracts are active against pathogens; *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Salmonella typhi*, *Shigella flexneri*, *Salmonella enteritidis*, *Vibrio cholerae* and *Shigella dysenteriae* (Toda et al., 1989). Studies show that catechins present in tea protect rabbits against infection caused by *V. cholerae* and also reports that there will be a benefit to cholera patients when tea extract is given as an oral rehydration solution (Dubreuil, 2013). Another Japanese report suggests that consumption of green tea will reduce dental caries in school children because of the polyphenolic content in tea (Hamilton-Miller, 1995). Studies suggest there is a positive effect of gut microbiota on administering tea extracts. In fat-induced mice, when administered with oolong tea polyphenols for four weeks, the following changes are seen: fecal microbiota diversity improved, reduces bacteroidetes, reduced obesity and showed insulin resistance (IR) (Bond and Derbyshire, 2019). On the other side, black, and green teas reduce cecum firmicutes and increased bacteroidetes. Reduction in diversity of gut microbiota had occurred when GTPs were administered to normal Sprague Dawley rats on a long-term basis. Reduction in the peptostreptococcaceae population and rise in bacteroidetes, *Oscillospira phylotypes* is due to the main content of EGCG present in GTPs (Sánchez et al., 2020). The whole plant extract is given as a food supplement to livestock to prevent intestinal diseases in livestock. Studies conducted on the composition of pig fecal microbiota resulted that the whole plant tea extract has the property to reduce some of the potentially pathogenic bacteria in the gut of the piglet and also promotes animal health (Bhatt et al., 2010).

65.3.5 ANTI-OBESITY ACTIVITY

Green tea catechins are responsible for reducing or preventing the increase in body weight of obese Zucker rats because of EGCG. Green tea supplementation helps in reducing body weight, liver fat accumulation, white adipose fat tissue, serum triglyceride levels, increases lysophospholipids levels and

energy expenditure. The anti-obesity level is mainly attributed to polysaccharides and all various types of catechins and polyphenols (Chacko et al., 2010). When tea was given along with vitamin E to male Syrian hamsters resulted in a reduction of plasma cholesterol concentration, low-density lipoprotein oxidation, and early atherosclerosis compared to tea consumption alone (Tijburg et al., 1997). Studies on mice reveal that black tea, oolong tea, green tea reduces body weight, total visceral fat volume, liver lipid weight. Black tea and green tea polyphenol will increase adiponectin gene expression (Heber et al., 2014). Oolong tea has a role in regulating fatty acid oxidation, energy expenditure, reducing body weight and fat deposition (Sánchez et al., 2020). Research on bioactive compounds in tea extracts shows that epigallocatechin-3-gallate plays a significant role in reducing body weight, increase serum lipid profiles and fat infiltration in liver tissue. Tea saponins improve gut microbiota alternation, reduces body weight in obese mice (Zhang et al., 2019). A study revealed that regular consumption of green tea extract with more catechins has a fat-reducing effect and decreases systolic blood pressure and low-density lipoprotein cholesterol. It proved that green tea extract is responsible for reducing obesity and the risk of cardiovascular diseases (Bansal et al., 2012). Studies proved that green tea extract helps to boost metabolism and burn fat (Chopade et al., 2008). Atherosclerosis, mainly coronary artery disease, is prevented by green tea because of its antioxidant properties. Green tea reduces total cholesterol (TC) and increases high-density lipoprotein, which is a good cholesterol in animals and humans (Chopade et al., 2008). Tea can also prevent respiratory diseases like shortness of breath, and wheezing caused by chronic bronchitis, asthma, and other lung diseases (Sharangi, 2009).

65.3.6 ANTI-HYPERSENSITIVE ACTIVITY

Among cardiovascular diseases, hypertension is the most common, which affects people all over the world. Epidemiological studies show that drinking green tea leads to a reduced risk of hypertension and lowers diastolic blood pressure; increased consumption of green tea decreases CVD mortality risk, mainly for coronary heart disease among Japanese women (Deka and Vita, 2011). O-methylated EGCG-contained tea has the most vigorous angiotensin-converting enzyme (ACE) inhibitory activity, which decreases systolic blood pressure. Thearubigin and theaflavin are responsible for all types of anti-hypertension properties (Persson et al., 2006). A clinical trial result shows that consuming one dL/day of tea will reduce systolic blood

pressure by 0.6 mm/Hg and pulse pressure by 0.5 mm/Hg (Sánchez et al., 2020). Another study showed that consuming black tea regularly for seven days decreases systolic blood pressure by 3.2 mm/Hg and diastolic blood pressure by 2.6 mm/Hg (Zhang et al., 2019).

65.3.7 ANTIOXIDANT ACTIVITY

Oxidative damage is ordinarily caused by increased free radicals' production by exogenous and endogenous sources. Recent studies show that free radicals damage affects all types of organs and tissues. Polyphenols in tea prevent the free radical formation and result in iron and copper metal formation by chelation process. Polyphenols also prevent interacting Nitrogen-containing compounds with the nitrosating agents that lead to the formation of offensive N-nitroso compounds (Mahmood et al., 2010). When black tea leaf extract was treated upon human red blood cells, it was proved to be effective against oxidative stress. Inducers like Cu^{2+} ascorbic acid, xanthine/xanthine oxidase system, phenylhydrazine are used to induce oxidative stress. At the same time, tea protects against the degradation of membrane proteins (Bhatt et al., 2010). Green tea contains tocopherols, carotenoids, ascorbic acid (vitamin C), minerals such as Mn, Se, Zn, Cr, and some phytochemical compounds responsible for its antioxidant activities (Chacko et al., 2010). Studies in mice show that green tea protects erythrocytes against acetaldehyde, tertiary butyl hydroperoxide, and ethanol (Zapora et al., 2009).

Studies reveal that catechins are present in both black and green tea. With budding yeast and fission yeast, a study was made and stated that polyphenols present in tea are used as prooxidants, which respond to oxidative stress in a weak alkaline condition (Maeta et al., 2007). When arsenite is induced to cause oxidative stress in Swiss albino mice, green, and black tea was effective against arsenite (Sinha et al., 2010). Gentamicin-treated rats induce nephrotoxic effects. When green tea extract was administered simultaneously, green tea extract protected the kidney tissues in rats against nephrotoxic effects (Abdel-Raheem et al., 2010). EGCG was found to have the highest total oxy radical scavenging capacity (TOSC) compared to other catechins present in tea (He et al., 2018). On the other hand, epicatechin-3-gallate was found to be the least effective among the catechins tested, mainly because of the presence of the gallate group at 3' positions which attributes to the antioxidant activity. In addition to that, adding hydroxyl group at 5' position in B ring increases the TOSC of catechins (Bansal et al., 2012).

65.3.8 GREEN TEA REDUCES TOOTH DECAY

Green tea has been shown to have the property of destroying the causative organism of dental plaque and caries. Dextran sucrase, glucosyltransferase enzymes are inactivated by green tea leading to the removal of insoluble glucan and lactic acid. Epigallocatechin in tea has the property to inactivate amylase in saliva and helps to decrease hydrolysis (starch to maltose), which leads to the reduction of acid erosion on teeth enamel (Goenka et al., 2013). Recent studies showed that people consuming tea had a reduction in tooth caries. Oolong tea has the power to reduce dental plaque. It also inhibits the growth of odor-producing bacteria in the mouth. In Beijing, a study was made with patients administered with green tea with oral leukoplakias that resulted in a reduced number of micronuclei, reduced precancerous mucosa lesions, and DNA aberrations in the lymphocytes (Li et al., 1999).

65.3.9 GREEN TEA AND ITS EFFECTS ON THE INTESTINE

Green tea catechins reduce nitrosating substances in gastric conditions, and it suppresses the nitrosation of susceptible secondary amines (Masuda et al., 2006). Intestinal microflora can also be altered by green tea. It alters microflora in the intestine and increases the bifidobacteria and lactobacilli growth in the gut wall. Consuming tea alters bacterial profiles in the intestine and disturbs the carcinogenic process in the intestine (Jung et al., 2019). In China, females who drink tea have a protective sheath that prevents the occurrence of rectal cancer. Studies show that patients who consume over 10 cups of green tea day per day have lower symptoms of colorectal cancer. Green tea was found to be protective against gastrointestinal mucosa (Yang et al., 2011). Reports on rats reveal that intake of 0.6% w/w green tea will prevent atrophy of intestinal mucosa and ensure quick healing of mucosal damage (Asfar et al., 2003). Green tea consumption has reduced the absorptive power of sugar and fat in a human clinical trial (Mousavi et al., 2013). The effect of tea catechins on bowel movement was studied in a trial conducted on healthy volunteers and proved that after taking 500 mg EGCG tablets for three months, there is an improvement in bowel movement (Koo and Cho, 2004).

65.3.10 GREEN TEA AND ITS DERMATOLOGICAL EFFECTS

Green tea helps recover from itching and inflammation of insects, bud bites, and stops profuse bleeding. The antiseptic property of tea is attributed to its tannins and flavonoids (Chan et al., 2011). Lab experimental studies in animal models proved that green tea extract, when supplied orally or rubbed on the

skin, inhibits skin tumor formation caused by chemical carcinogens and UV radiation. EGCG in tea protects the mouse skin against UVB-induced oxidative stress and suppresses the immune system (Katiyar, 2003). Nowadays, more pharmaceutical and cosmetic companies use green tea as one of the ingredients to manufacture their skin care products (Namita et al., 2012).

65.3.11 ANTIHISTAMINIC ACTIVITY

Tea extract has also proved to have antihistaminic activity in murine peritoneal mast cells. In murine cell culture, tea polyphenols will be able to control histamine production to 90%. Anti-histaminic and anti-inflammatory properties in black tea are because it has 54%–7% of quercetin-type flavonol glycosides. Thus, it is used as a therapeutic against asthma (Naveed et al., 2018).

65.3.12 GREEN TEA AND ITS EFFECT ON BRAIN

In the biosynthesis of biogenic amine, L-dopa is converted into dopamine and serotonin, which is done by an enzyme called dopa decarboxylase; when polyphenols of green tea such as EGCG and epigallocatechin bind to the enzyme's active site, inactivates the enzyme dopa decarboxylase by following the pseudo-first kinetics at a fixed concentration of EGCG (Bertoldi et al., 2001). A test was done on rats to check neuromuscular blocking action of botulinum neurotoxin types of A, B, E in phrenic nerve diaphragm of rats. It indicated that thearubigins mixed with each neurotoxin protected against the neuromuscular blocking action of neurotoxin types A, B, E by binding with the toxin (Satoh et al., 2002).

KEYWORDS

- ***Camellia sinensis***
- **epicatechin gallate**
- **epigallocatechin**
- **green tea**
- **polyphenols**
- **neuromuscular blocking action**
- **anti-inflammatory**
- **thearubigins**

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CHAPTER 66

An Outline of Bioactive Constituents and Pharmacology of Caper Bush (*Capparis spinosa* L.)

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66.1 INTRODUCTION

Capparis spinosa comes under the Capparaceae family. The common name of *Capparis spinosa* is Caper. Caper bush belongs to the xerophytic species, which has a good capacity of adaption to harsh and drought environments. It is well known for its flower buds (edible) and fruits (widely used as pickles). *Capparis spinosa* has an excellent water use efficiency (WUE) among other desert plants and a unique capacity to absorb water through its effective root system with an exceptional root-stem ratio (Zuo et al., 2012; Gan et al., 2013). *Capparis spinosa* can be used as an ornamental plant for its esthetic and sweet-scented flowers. The Caper bush plant is a perennial shrub with white/white-pinkish flowers. Ellipsoidal, oblong, or obovate fruits with numerous reddish-brown seeds are present in the Caper plant (Fici, 2014). The flower bud is the economic part of this plant, commonly known as "Capers" or "Caperberry." *Capparis spinosa* plays a vital role in caring for the health of human beings. Caper bush plant can be grown to prevent land degradation and control erosion problems through its extensive root system. In the world, 15–20 tons/year of production is noticed in the Caper bush plant, and the top-most producers and exporters of the *Capparis spinosa* are Morocco and Turkey (Infantino et al., 2007).

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66.2 BIOACTIVES

The bioactive chemicals present in the *Capparis spinosa* has been investigated by many researchers through its extract by various methods. Secondary metabolites such as flavonoids and phenolic compounds are rich in the Caper bush plant, which play an essential role in the abiotic stress response, especially heat tolerance. *Capparis spinosa* contains glucosinolates (glucoiberin, glucobrassicin, glucocapparin, sinigrin), phenolic acids, flavonoids (kaempferol, rutin, quercetin) and alkaloids (Sozzi and Vicente, 2006; Kulisic-Bilusic et al., 2012; Francesca et al., 2016). The hydrolysis products present in *Capparis spinosa* are very well known for their anti-cancer property (Mithen et al., 2000). The composition of glucosinolate in *Capparis spinosa* ranges from 84% to 89%. In shoots and buds, glucocapperin (methyl glucosinolate) is present, whereas, in leaves and shoots, a trace amount of indole glucosinolate (4-hydroxy-glucobrassicin) is present. Seeds and leaves of *Capparis spinosa* contain glucocapparin and glucocleomin (Matthäus and Ozcan, 2002). Few organic acids and a newly identified antioxidant compound are found in the fruits of *Capparis spinosa* (Yang et al., 2010a, b). In China, few more bioactive compounds like hypoxanthine, adenosine nucleoside and uracil were extracted from the fruits of *Capparis spinosa* and the identified compounds stachydrine and capparilloside A (Fu et al., 2007). From the fruits, the roots and the leaves of *Capparis spinosa*, 22 essential oil components were isolated (Afsharypuor et al., 1998). The extract of Caper bush plant leaves led to the isolation of 14 different components of essential oil. Four essential components constituting the composition of the essential oil from the leaf extract are isopropyl isothiocyanate (11%), butyl isothiocyanate (6.3%), thymol (26.4%), 2-hexenal (10.2%). Only four different essential oil components can be extracted from the fruits of *Capparis spinosa*. Among these four components, isopropyl isothiocyanate (52.2%) and methyl isothiocyanate (41.6%) contribute to the primary components of the essential oil. The major essential oil components extracted from the roots of the Caper bush plant are isopropyl isothiocyanate (31.4%) and methyl isothiocyanate (53.5%). In Croatia, methyl isothiocyanate (92.06%) is observed as a vital component contributing to the significant part of the essential oil extraction from the leaves and flower buds of *Capparis spinosa*, along with the sec-butyl isothiocyanate (0.25%), benzyl isothiocyanate (0.74%), butyl isothiocyanate (0.38%) and benzene acetonitrile (0.40%) (Kulisic-Bilusic et al., 2010). In fruits and roots of *Capparis spinosa*, methyl isocyanate and isopropyl isothiocyanate are the significant components. In contrast, the butyl-isothiocyanate is the tissue-specific component, and it

occurs in the leaves but is absent in the fruits and roots. The component glucosinolate breaks down into thiocyanate and isothiocyanate as methyl glucosinolate (glucocapperin) with the help of catalyst myrosinase enzyme, which passes by the intermediate thiohydroximate, and a component methyl isothiocyanate is produced during the rearrangement process (Sozzi and Vicente, 2006). The chemical structure of phytochemicals and essential oil components of *Capparis spinosa* are given in Figure 66.1.

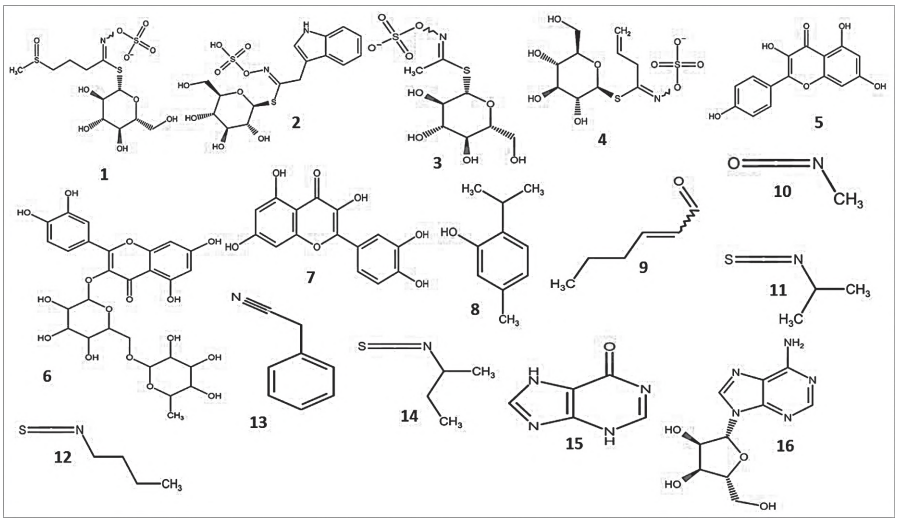


FIGURE 66.1 Chemical structures of bioactive compounds and essential oil components of *Capparis spinosa*. Glucoiberin (1); glucobrassicin (2); glucocapparin (3); sinigrin (4); kaempferol (5); rutin (6); quercetin (7); thymol (8) and 2-hexenal (9); methyl isocyanate (10); isopropyl isothiocyanate (11); butyl isothiocyanate (12); benzene acetonitrile (13); sec-butyl isothiocyanate (14); hypoxanthine (15); and adenosine (16).

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

66.3 PHARMACOLOGY

66.3.1 ANTI-HYPERGLYCEMIC ACTIVITY

Anti-hyperglycemic activities are widely observed in the extracts of *Capparis spinosa* (Eddouks et al., 2005; Lemhadri et al., 2007). In Iran, diabetic patients consume the Caper fruit as a traditional anti-diabetic food. The decline in the blood sugar and triglycerides level was observed in the diabetic rats due to the intake of *Capparis spinosa* fruit extract (Rahmani et al., 2013). In Iran, a decline in the glucose level and glycosylated hemoglobin level in the blood was identified on type 2 diabetic patients due to the ethanol

extract of *Capparis spinosa* fruits, and also the triglyceride level decreased in the blood, proving the results of the Caper bush plant's anti-hyperglycemic activity and hypolipidemic activity (Huseini et al., 2013). The process of pancreatic α-amylase activity is inhibited due to the ethanolic extract (EE) of both root and leaf of the Caper bush plant, which resulted in blood sugar control. No side effects, no kidney and liver damage were observed due to the usage of *Capparis spinosa*. The Caper bush plant's anti-hyperglycemic activity effects are due to the obstruction of gluconeogenesis in the liver, reduced absorption of carbohydrates from the small intestine, promoting glucose uptake by the tissues and rejuvenation or protection of beta cells (Selfayan and Namjooyan, 2016).

66.3.2 ANTI-INFLAMMATORY ACTIVITY

During the inflammation process, cartilage degeneration is blocked by anti-inflammatory agents produced from the lyophilized extracts of *Capparis spinosa* flower buds (LECS). It gives protection to the chondrocytes (Panico et al., 2005). The Caper plant's fruit and leaf extract showed a significant anti-inflammatory activity than the root extract (Zhou et al., 2010; Hong-Juan et al., 2014). The active anti-inflammatory compounds isolated from the aqueous extract of the Caper fruit also act against anti-arthritic activity (Feng et al., 2011; Jiang et al., 2015). For treating the disorders like rheumatism, *Capparis spinosa* is used as traditional medicine. Few scientific studies showed that a specific dose of *Capparis spinosa* is non-toxic. An appropriate dose of *Capparis spinosa* increases cell metabolism activity by not affecting the cell proliferation process. When 100 and 500 microgram/ml dose of aqueous extract of *Capparis spinosa* is treated against peripheral blood mononuclear cells (PBMCs), an anti-inflammatory response is produced through critical processes like IL-17 inhibition and commencement of IL-4 gene expression. The presence of anti-inflammatory agent spermidine alkaloids in the root extract of *Capparis spinosa* is used to cure the pain of rheumatoid arthritis and osteoarthritis (Maresca et al., 2016). The dermis tissue's thickness and immune cell infiltration at the inflammatory site are lowered by the Caper bush plant extract (El-Azhary et al., 2017). When the Caper bush plant flower buds are taken, an anti-inflammatory response is produced by lowering the concentration of nitric oxide (NO), prostaglandins (PGE2) and reactive oxygen species (ROS), which IL-1β produces on chondrocytes in the human body system (Panico et al., 2005).

66.3.3 ANTIOXIDANT ACTIVITY

The methanolic extract of Caper fruit berries exhibits a significant antioxidant response, especially on the cancer-causing carcinoma cells of the liver (Yu et al., 2017). The Caper extract decreases the effect of the cancer-causing agent doxorubicin by protecting the cardiovascular system (Mousavi et al., 2016). *Capparis spinosa* is very rich in flavonoids, which are potent antioxidants that prevent cancerous tumors. Few scientific studies showed that flavonoids lower the growth and proliferation of specific cancer cells. The Caper protein can stop the breast cancer cells, hepatoma HepG2 proliferation and colon cancer cells (Lam and Ng, 2009; Lam et al., 2009).

66.3.4 ANTI-HYPERTENSIVE ACTIVITY

Capparis spinosa can be used for the treatment of hypertension. When the hypertensive rat models are administered with the extract of Caper fruit, the blood pressure is reduced with the gradual increase in the urine's potassium, chloride, and sodium concentration. The heartbeat rate is regular with no changes (Ali et al., 2007).

66.3.5 ANTI-MICROBIAL ACTIVITY

The Caper plant extract shows significant antifungal activity against *Valsa mali*; *Valsa mali* is a necrotrophic fungus of Ascomycete. Infection induces Valsa canker on apples, a devastating epidemic of apples in Eastern Asia (Lam and Ng, 2009; Lam et al., 2009). The extract from the Caper bush plant root shows a significant effect of antibacterial activity against many bacteria like *Streptococcus mutans, Staphylococcus saprophyticus, Streptococcus pyogenes, Staphylococcus aureus,* and *Staphylococcus epidermidis* (Mahboubi and Mahboubi, 2014).

The root extract of *C. spinosa* exhibits antibacterial activity towards *Deinococcus radiophilus* by stopping its growth process (Boga et al., 2011). The aqueous extract of the Caper plant root makes *Escherichia coli* stop proliferating (Boga et al., 2011). *Capparis spinosa* root extract shows significant antibacterial and antifungal activity against many fungi and bacteria like *Aspergillus parasiticus, Aspergillus flavus, Aspergillus niger, Candida glabrata, Candida albicans, Escherichia coli, Bacillus subtilis, Salmonella typhimurium, Shigella dysenteriae, Bacillus cereus, Shigella flexneri* and

Klebsiella pneumoniae (Mahboubi and Mahboubi, 2014). The Caper bush plant fruit extract also inhibits the growth rate of *Pasteurella multocida* (Gull et al., 2015).

66.3.6 ANTI-VIRAL ACTIVITY

The proteins purified from the *Capparis spinosa* fruit seeds stop the HIV-1 reverse transcriptase (RT) activities (Lam et al., 2009). Human immunodeficiency virus (HIV)-1 RT can be inhibited by the Caper bush plant extract. The N-terminal amino acid sequence of the protein identified from the Caper bush plant seeds helps in HIV-1 RT inhibition. Imidazole glycerol phosphate synthase possesses some properties similar to the protein isolated from *Capparis spinosa* (Lam and Ng, 2009).

66.3.7 ANTIHEPATOTOXIC ACTIVITY

Capparis spinosa root bark extract protects the liver against carbon tetrachloride, which is toxic (Aghel et al., 2010). P-methoxy benzoic acid isolated from *Capparis spinosa* exhibits an antihepatotoxic response (Aghel et al., 2010; Gadgoli and Mishra, 1999). In the treatment of many cancers, Cisplatin is used as a significant drug that causes damage to both the liver and kidney. Recent studies showed that *Capparis spinosa* leaves extract protects the liver and kidney in cancer treatment along with Cisplatin drug (Tlili et al., 2017).

66.3.8 ANTI-OBESITY ACTIVITY

When the diabetic rats consumed the aqueous extract of Caper bush plant fruits, there was a decrease in their body weight (Eddouks et al., 2005). Oral intake of *Capparis spinosa* extract repeatedly lowers the body weight of high-fat diet rats (Lemhadri et al., 2007). The Caper bush plant helps in the improvement of plasma lipid parameters. *Capparis spinosa* fruit extract helps people with type-2 diabetes by lowering the triglyceride level in the blood (Huseini et al., 2013). *Capparis spinosa* inhibits gluconeogenesis in the liver and is used for treating many liver diseases and metabolic syndrome. *Capparis spinosa* reduces the cholesterol level by lowering 3-hydroxy-3-methyl-glutaryl coenzyme A reductase activity. This reductase plays an essential role in the cholesterol biosynthesis process (Ness, 2015).

KEYWORDS

- **caper bush**
- ***Capparis spinosa***
- **glucosinolates**
- **human immunodeficiency virus**
- **isothiocyanate**
- **peripheral blood mononuclear cells**

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CHAPTER 67

Bioactives and Pharmacology of Papaya (*Carica papaya* L.)

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67.1 INTRODUCTION

Carica papaya L. is from the family Caricaceae, and it is widely grown in tropical and subtropical zones of the world (Silva et al., 2007). *Carica papaya* is generally called papaya. Its small part of the genome shows peculiarities in major gene groups involved in photoperiodic responses, carbohydrate economy and secondary metabolites, cell size, and lignification, which place them intermediate between trees and herbs (Jiménez et al., 2014). Papaya was a popular fruit in most parts of the American continent. It was first discovered by the Spanish people in the area between the southern part of Mexico and the Northern part of Nicaragua (Alara et al., 2020). Papaya is considered a powerhouse of nutrients and rich in three crucial antioxidants: Vitamin E, Vitamin C, and Vitamin A. The essential papaya nutrients protect the body against heart diseases, improve the cardiovascular system, and prevent heart attacks, colon cancer, and strokes (Vij and Prashar, 2015). Traditionally, papaya leaves were used to treat jaundice, malaria, dengue, warts, sinuses, eczema, cutaneous tubercles, blood pressure, dyspepsia, constipation, amenorrhea, and expel worm, immunomodulatory, and antiviral activity (Yogiraj et al., 2014). Breast milk is increased in lactating women when fomenting breasts with hot papaya leaves, and fresh leaves of papaya are gargled to cure gingivitis, ulcerative, and tonsillitis (Priyadarshini and Ram, 2018). Papaya is a fast-growing, semi-woody tropical herb, and the stem is hollow, single,

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and straight with prominent leaf scars (Silva et al., 2007). Ripe papaya is consumed as a favorite breakfast in various places, and it is also used to prepare refreshing drinks, jam, fruit salad, crystallized fruit, candies, and marmalade. Unripe Papaya fruits are cooked as a vegetable, young leaves are eaten as a medicine, flowers are used to make sweetmeat, and papaya seeds are used as abortifacient and vermifuge (Villegas, 1997).

67.2 BIOACTIVES

Current findings indicate that ascorbic acid, phenolic compounds, and carotenoids are functional compounds that defend the organism from the generation of ROS and lower the risk of heart disease and certain cancers. HPLC and mass chromatography examination were done in four phases of maturity of papaya to analyze the principal phytochemicals contained in the pulp or peel of the fruits. Caffeic acid, ferulic acid, and p-coumaric acid were the chemicals discovered. Lycopene, β-criptoxanthin and β-carotene were among the carotenoids that increase in the flesh as the fruit matures and along with vitamin C. Phenolic compounds found in the fruit peel tends to diminish as the fruit ripens. These findings suggest that the maturity phase significantly impacts the concentration of functional chemicals in papaya (Sancho et al., 2011). The young leaves of papaya plants are rich in alkaloids such as dehydrocarpaine I and II, carpaine, pseudocarpaine; flavonoids (kaempferol and myricetin); cynogenetic compound (benzylglucosinolate); phenolic compounds (caffeic acid, chlorogenic acid, ferulic acid) and carotenoids, namely lycopene, β-carotene, and anthraquinone glycosides, which shows therapeutic characteristics viz., for fertility issues, known to be anti-inflammatory, hypoglycemic, hepatoprotective, abortifacient, and heals cuts and wounds (Yogiraj et al., 2014). The papaya leaves also have additional phytochemical compounds, including anthraquinone, phlobatanin, cardiac glycosides, proathocyanidin, and saponin (Yusha'u et al., 2009). The papaya fruit has a juicy yellow flesh characterized by a high content of hydroxycinnamic acid, proteolytic enzyme papain and chymopapain and quercetin glycoside derivatives, which plays a significant role in antioxidant, anti-hyperglycemic, and insulin stimulating activities (Vega-Gálvez et al., 2019). Papaya also has other bioactive like zeatin, vitamin K, other phytoconstituents like aromatic amino acids, polyphenols, sugars, phytosterols, sulfur-containing amino acids and nutrients like iron, calcium, magnesium, sulfur, and potassium (Saha and Giri, 2019). The seeds of Papaya fruit contain fatty acids, crude protein, carpaine, benzylisocyanate, benzylglucosinolate,

glucotropacolin, caricin, benzylthiourea, and hentriacontane (Krishna et al., 2008) (Figure 67.1).

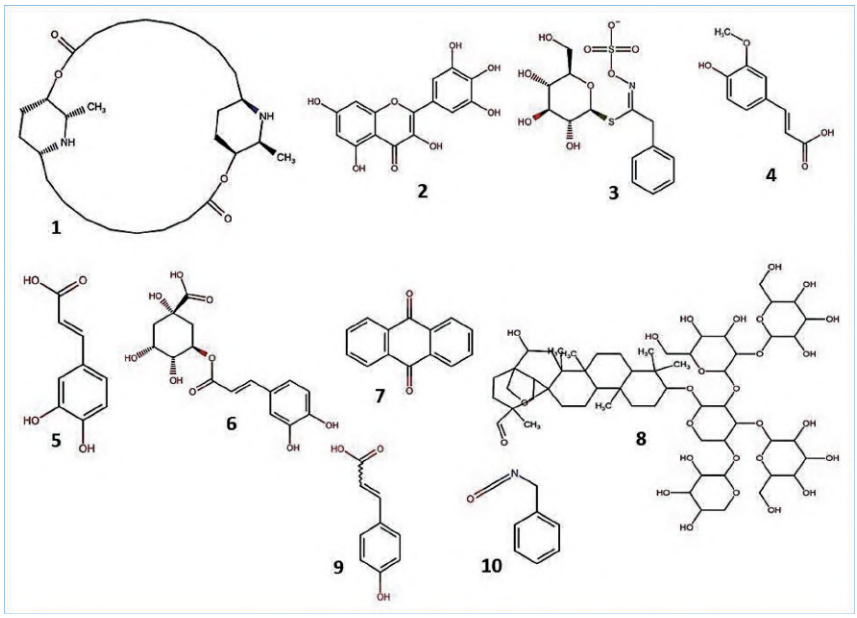


FIGURE 67.1 Few major compounds present in *Carica papaya*. Carpaine (1); myricetin (2); benzylglucosinolate (3); ferulic acid (4); caffeic acid (5); chlorogenic acid (6); anthraquinone (7); saponin (8); hydroxycinnamic acid (9); and benzylisocyanate (10).

67.3 PHARMACOLOGY

67.3.1 ANTIFUNGAL ACTIVITY

Fluconazole and latex of papaya show synergistic action on inhibiting the growth of *Candida albicans* (Krishna et al., 2008). Papaya seeds essential oil possesses promising character in anti-candida activity, which shows inhibitory effect against *Candida parapsilosis, Candida tropicalis, Candida albicans, Candida glabrata* and *Candida krusei* (Kaur et al., 2019). Boiled leaf extracts of papaya show an inhibiting effect against five dermatophytic fungi (*Trichophyton rubrum, Trichophyton mentagrophytes, Micosporum gypseum, Trichophyton tonsurans, Microsporum canis*), six saprophytic fungi (*Rhizopus* sp., *Fusarium* sp., *Penicillium* sp., *Helminthosporum* sp., *Aspergillus niger* and *Aspergillus flavus*) and six yeasts (*Candida tropicalis, Candida kruzei, Candida albicans ATCC 0383, Candida galbrata*, *Candida albicans* and *Saccharomyces*) (Alara et al., 2020).

67.3.2 ANTI-MICROBIAL ACTIVITY

The papaya fruit pulp and seeds show antimicrobial activity against *Trichomonas vaginalis trophozoites* and gastrointestinal bacterial infections such *as Klebsiella pneumoniae, Enterobacter cloacae, Pseudomonas aeruginosa, Proteus vulgaris, Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Salmonella typhi* (Alara et al., 2020). The leaf extracts of papaya have antimicrobial activity against *Pseudomonas aeruginosa,* and the methanolic leaf extracts have antimicrobial activity against *Candida abicans, Staphylococcus aureus* and *Escherichia coli* (Wadekar et al., 2021). In a study, a pure component derived from *Carica papaya* seed was evaluated *in vivo* versus live fish, *Channa punctatus*, challenged with bacterial isolates of *Klebsiella* PKBSG14 at a level of 0.75 CFU/ml. The isolated natural component was identified to be oleic acid, $C_{18}H_{34}O_2$. This molecule was then tested *in vivo* for its activity as an effective antibacterial using genotoxicological and cytotoxicological assays. A dose of 0.5 mg/kg and 1 mg/kg b.w. of pure isolated oleic acid was evaluated and found to be efficient in causing DNA Strand breaks, comet tail length, and toxic indicators such as oxidant production. *In vivo* experiments revealed comparable properties on splenic cells in terms of viable cells as measured by cell cycle analysis, PI staining and the Annexin-FITC experiment. Altogether, these findings indicate that oleic acid enhances therapeutic absorption and thus has a superior chemo-preventive activity towards pathogenic bacteria *in vivo* (Ghosh et al., 2017).

67.3.3 ANTHELMINTIC ACTIVITY

The consumption of air-dried papaya seeds as an elixir with honey showed a significant effect against human intestinal parasites due to the presence of benzyl isothiocyanate (Krishna et al., 2008). The latex of papaya shows anthelmintic efficiency due to the synergetic action of dehydro-carpaines and carpaine enzyme (Kaur et al., 2019). The anthelmintic property shown by papaya gives a cheap, cost-effective, and straightforward way of treating gastrointestinal parasites without any side effects (Alara et al., 2020). Applying papaya leaves paste with common salt and opium for three days helped the easy extraction of worms from the body (Priyadarshi and Ram, 2018). The proteolytic enzymes present in papaya extracts are known to digest nematode cuticles, and it has been traditionally used as a medicine against gastrointestinal nematodes (Nakhate et al., 2019).

67.3.4 ANTIMALARIAL ACTIVITY

The protozoa parasite of the genus *Plasmodium* causes an infectious disease called malaria (Alara et al., 2020). It is observed that the petroleum ether extract of the rind of the papaya fruit has an antimalarial activity (Adiaha and Adiaha, 2017). The leaf extracts of papaya exhibit high antiplasmodial activity with low cytotoxicity, which gives the capability of papaya leaves to cure malaria (Priyadarshi and Ram, 2018). The leaves of papaya are made into a tea and given to the treatment of Malaria (Begum, 2014).

67.3.5 ANTI-INFLAMMATORY ACTIVITY

The extensive range of secondary metabolites (alkaloids, flavonoids, saponins, and flavanoids) present in papaya can reduce inflammatory reactions in the body (Wadekar et al., 2021). The anti-inflammatory action of protein compounds (chymopapain and papain) and some antioxidant nutrients (vitamin E, betacarotene, and vitamin C) present in papaya were accounted in reducing the effect of rheumatoid joint inflammation, osteoarthritis, and asthma in affected patients (Alara et al., 2020).

67.3.6 WOUND HEALING PROPERTY

Papain present in the latex papaya is a nonspecific cysteine proteinase that can break down a wide variety of necrotic tissue substrates over a wide range of pH, contributing to faster wound healing in the body (Nakhate et al., 2019). In addition, the latex also reduces the risk of oxidative destruction to tissue and is also helpful in burn healing activities by increasing hydroxyproline constituents (Alara et al., 2020). The aqueous extract of papaya fruit (100 mg/(kg.d) for 10 d) has a potent wound healing property (Vij and Prashar, 2015).

67.3.7 ANTICANCER PROPERTY

The aqueous extract of papaya leaves (0.625–20 mg/mL) shows anti-tumor activity and inhibit the proliferated responses of solid tumor cell lines derived from breast adenocarcinoma (MCF-7), pancreatic epithelial carcinoma (Panc-1), hepatocellular carcinoma (HepG2), mesothelioma (H2452), cervical carcinoma (Hela) and lung adenocarcinoma (PCI4) in a dose-dependent manner (Vij and Prashar, 2015). The papain enzyme present in papaya is effective against cancer by breaking down the fibrin cancer cell wall and protein into amino acid form (Nakhate et al., 2019). Papain in papaya fruit

contains a pigment called lycopene, which is highly reactive towards free radicals and oxygen. The isothiocyanate in papaya protects from prostate, pancreas, breast, leukemia, colon, and colon lung cancer (Wadekar et al., 2021). The papaya leaves containing tannins, rutin, alkaloids, resin, saponins, and dehydrocarpaines showed cancer-fighting properties against a broad spectrum of tumors causing cancers (Kaur et al., 2019). The papaya fibers can bind cancer-causing toxins in the colon and separate them from healthy colon cells (Begum, 2014). The tea made by papaya leaves significantly reduced cancer cell growth and boosted Thi-type cytokine that regulates the immune system. The ME of Papaya black seed showed a significant reduction in cell proliferation of PC-3 cells (Alara et al., 2020).

67.3.8 ANTI-SICKLING ACTIVITY

The disease sickle cell anemia occurs when there is a sudden change in the hemoglobin structure of red blood cells where the sixth position of glutamine amino acid is replaced by valine (Alara et al., 2020). A recent study showed an antis-sickling activity when unripe papaya fruit extract is given to the affected patients (Nakhate et al., 2019). Under osmotic stress conditions, the methanolic extract of papaya at a dose of 10 mg/ml reduced hemolysis and erythrocyte membrane integrity (Vij and Prashar, 2015). There is an increase in urine output and shows similar profiles of urinary electrolyte excretion to that of hydrochlorothiazide when aqueous root extract of papaya is given orally to the rats at a dose of 10 mg/kg (Nakhate et al., 2019).

67.3.9 ANTI-DENGUE ACTIVITY

Dengue fever is a tropical disease caused by the dengue virus. It is mainly spread through mosquitos *Aedes aegyptii*, in which the mosquitos act as a vector in transmitting the disease (Ashok and Mol, 2017). The leaf extracts of papaya contain membrane-stabilizing properties and protect blood cells from stress-induced destruction, which is significantly helpful for patients infected by the dengue virus prevent platelet lysis. This effect is observed due to the presence of phenolic compounds and flavonoids present in the leaves of Papaya (Nakhate et al., 2019). The aqueous extract of papaya leaves shows potential activity against dengue fever (Priyadarshi and Ram, 2018). In a study, it was found that dengue affected patients taking papaya leaf extract tablets thrice a day for five days showed a significant increase in platelet count within the 24 hours of consumption of tablet, and this was

observed due to the presence of gene responsible for platelet construction called platelet-activating factor (PAF) receptor gene in the papaya leaf extract capsules (Wadekar et al., 2021). The recently available drug for treating dengue is Caripill, which is in the formulation of syrups and tablets of leaf extract of papaya in which syrup contains 275 mg/5 ml and tablet contains 1,100 mg of papaya leaf extract (Ashok and Mol, 2017).

67.3.10 FEMALE ANTI-FERTILITY

Controlling human fertility has been a significant social challenge faced by humanity over the years. Continuous use of synthetic contraceptive drugs showed adverse side effects in the body. Recent studies show that seed extract of papaya has contraceptive effects in male and female rats and mice (Alara et al., 2020). There was a morphological change in the endometrial surface epithelium of the albino rat uterus when a composite root extract containing papaya was given. Papaya shows abortifacient and anti-implantation effects inside the body. Feeding adult and pregnant rats with papaya fruit were done to investigate papaya fruit's antifertility properties (Nakhate et al., 2019). The consumption of semi-ripe or unripe papaya during pregnancy is unsafe because the unripe papaya contains a high concentration of latex which induces marked uterine contractions (Begum, 2014).

67.3.11 MALE ANTI-FERTILITY

Papaya seeds contain antifertility bioactive compounds such as triterpenoids and saponins. In a study, treatment with papaya seeds for seven days showed a reduction in sperm motility, concentration, and viability (Alara et al., 2020). The crude bark extract of papaya at a dose of 5–10 ml/(kg.d) given to the rats for four weeks on seminiferous tubules resulted in complete loss of fertility, attributing to a decline in sperm motility and change in their morphology and at the end, it was concluded that bark extract of papaya is a safe and effective male contraceptive that can be used in animals without any side effects (Vij and Prashar, 2015). In a study, male rats were treated with seed extract of papaya showed a gradual degeneration of Leydig cells, Sertoli cells, and germinal epithelium, which concludes that there is antifertility activity. The benzene chromatographic fraction of the chloroform extract (CE) of papaya seed shows a reversible male contraceptive potential, and this effect is mediated through testis (Begum, 2014).

67.3.12 HYPOGLYCEMIC ACTIVITY

In a study, streptozotocin (STZ)-induced diabetic rats were treated by oral administration of chloroform leaf extracts of papaya at a dose of 0, 31, 62, and 125 mg/kg. The result after the biochemical test showed that there was a significant reduction in transaminase, triglyceride, and blood glucose levels in diabetic rats. This study clearly showed hypoglycemic activity in leaf extracts of papaya (Alara et al., 2020). There is significant blood sugar level reduction when ethanolic leaf extract of papaya is given at a dose of 5 mg/kg, and there is no blood sugar level reduction when the dose is 10 mg/kg. The extract delays the onset of hypoglycemic activity of glimepiride and increases the anti-diabetic effect of metformin, with variables interacting adversely for each combination of drug extract (Vij and Prashar, 2015). The green papaya had been reported as a critical source of healing therapy for diabetic wound and diabetic patients (Alara et al., 2020).

67.3.13 ANTIDIARRHEAL ACTIVITY

Against the gut pathogens, the acetone extract of ripe papaya (25–0.39 mg/ml) and CE of raw papaya (25 mg/ml) show significant antidiarrheal activity. Ripe papaya extract extensively shows antidiarrheal properties against *Plesiomonas shigelloids* with a concentration range of 0.39 mg/ml–50 mg/ml. The herbal mixture of young bark of *Mangifera indica* and dried root of papaya is used in the treatment of diarrhea (Wadekar et al., 2021).

KEYWORDS

- **adenocarcinoma**
- **antifungal activity**
- ***Carica papaya***
- **dehydrocarpaine**
- **mass chromatography**
- **papain**

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CHAPTER 68

Phytochemistry and Pharmacological Properties of Saffron (*Crocus sativus* L.)

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68.1 INTRODUCTION

Crocus sativus L., a perennial herb belonging to the family Iridaceae, is a well-known spice, often referred to as the 'Red Gold' in producer countries (Mykhailenko et al., 2019). This autumn-flowering plant is the most expensive cultivated herb in the world, with a price tag of up to 1,000 $/kg. The plant is native mainly to the Mediterranean region and is cultivated widely in many countries, including India, Iran, Greece, and Spain (Zargari, 1990). Small-scale cultivation areas are found in countries like Italy, France, the United Kingdom, Afghanistan, Argentina, and New Zealand, by either farmers or private companies (Karabagias et al., 2017). Saffron has been valued since ancient times as a culinary condiment, as a source of dye, perfume, and also as medicine**.** Flowers, mainly the stigma of the saffron crocus (*Crocus sativus*), is used for harvesting saffron. Each flower has three stigmas and these threads of stigmas which are separated and dried constitute the saffron spice. To yield 1 kg of pure saffron, about 1,50,000–2,00,000 flowers need to be harvested by hand. Cultivation, harvesting, flower picking, and stigma separation makes the spice costly (Aytekin and Acikgoz, 2008). Blooming once in a year, saffron should be collected within a very short duration that is during 3–4 weeks in October to November. The species reported to be a sterile triploid, lacks fertile seeds. Germination of seeds is difficult and

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flowering of plants from seeds, takes up to three years (Al-Snafi, 2015). It propagates only vegetatively through corms (Brighton, 1977; Fluch et al., 2010).

Apart from use as a spice and dye, the plant is found to be effective against rheumatism, alcohol addictions, scarlet fever, smallpox, colds, asthma, eye, and heart diseases, tumor, cancer, respiratory decongestant, anodyne, emmenagogue, aphrodisiac, diaphoretic, antispasmodic, expectorant, and sedative, painkiller during delivery, as an aphrodisiac, antispasmodic, antiapoptotic, and anticarcinogenic and in treatment of kidney and urinary disorders in many tribal communities of India (Zareena et al., 2001; Akhondzadeh et al., 2005; Yu-Zhu et al., 2008; Ballabh et al., 2008; Fernández-Sánchez et al., 2012). In view of its wide economic perspective, extensive phytochemical studies have been done in saffron and a variety of bioactive constituents have been isolated. More than 150 volatile compounds have been reported in saffron stigmas including terpenes, terpene alcohols and their esters (Samarghandian and Borji, 2014). Non-volatile compounds like lycopene, zeaxanthin, and some α- and β-carotenes coming under class carotenoids, have also been reported. Among the biologically active compounds, the three major ones are crocin, picrocrocin, and safranal, which are contributing for saffron's organoleptic profile, namely color, taste, and odor, respectively (Alavizadeh and Hosseinzadeh, 2014). Studies conducted worldwide revealed that the species possess many pharmacological properties like antioxidant, anticonvulsant, antitussive, antidepressant, antihypertensive, cardioprotective, anti-inflammatory, antidiabetic, antinociceptive, anticancer, hepatoprotective, etc. (Srivastava et al., 2010). The current review focuses on important bioactive ingredients and pharmacological properties of saffron.

68.2 BIOACTIVE CONSTITUENTS OF *C. SATIVUS*

The major phytochemicals in saffron include secondary metabolites like carotenoid compounds, terpenoids, flavonoids, phenols, nitrogen-containing compounds, phytosterols, anthocyanins, anthraquinones, acetophenones, saponins, and also primary metabolites.

68.2.1 APOCAROTENOIDS AND ITS DERIVATIVES

Crocetin ($C_{20}H_{24}O_4$), a water-soluble apocarotenoid, crocin ($C_{44}H_{64}O_{24}$), a crocetin derivative and fat-soluble compounds like zeaxanthin, phytoene,

alpha-, and beta-carotene, lycopene, phytofluene are the major apocarotenoid compounds identified in saffron stigmas (Pfander and Schurtenberger, 1982; Tung and Shoyama, 2013; Grosso, 2016). Crocetin and crocin are used as coloring agents in foods and food products (Giorgi et al., 2017). In 1982, Pfander and Schurtenberger isolated six crocins from saffron stigma for the first time. Speranza et al. (1984) identified the isomers of crocins using HPLC and spectrophotometry. Tarantilis et al. (1995) identified numerous crocins in saffron stigma. Carmona et al. (2006a, b) reported some new crocins, and simplified the nomenclature of glycosidic esters. As reported by Llorens et al. (2015), trans-crocetin di-(β-D-gentiobiosil) ester (*trans*-4GG), trans-crocetin (β-D-glucosil)-(β-D-gentiobiosil) ester (*trans*-3Gg) and trans-crocetin (β-D-gentiobiosil) ester (trans-2G) are the prominent crocin esters in *C. sativus*. In 1989, Ghosal et al. identified mangicrocin, a xanthone-carotenoid glycosidic conjugate from saffron stigma. Trans-crocetin-1-al 1-O-β-gentiobiosyl ester, a new carotenoid glycoside was isolated from stigma (Tung and Shoyama, 2013).

68.2.2 MONOTERPENOIDS

Picrocrocin and safranal are the monoterpenoid compounds contributing to the bitter taste and aroma of saffron, respectively (Tarantilis and Polissiou, 1997). Safranal ($C_{10}H_{14}O$), is a monoterpene aldehyde derived from its precursor picrocrocin ($C_{16}H_{26}O_7$). Maggi et al. (2010), reported safranal as the major compound in saffron essential oil. Other major monoterpenoid compounds reported from essential oil in saffron are β-isophorone, α-pinene, 1,8-cineole, β-ionone (Tarantilis and Polissiou, 1997; WHO, 2003; Lage et al., 2015). Tung and Shoyama (2013) isolated a new safranal glycoside, (4R)-4-hydroxy-2,6,6-trimethylcyclohex-1-enecarbaldehyde 4-O-[β-D-glucopyranosyl (1→3)-β-D-glucopyranoside] from the stigma. 4-oxoisophorone, oleic acid, linoleic acid, palmitic acid, stearic acid (Tarantilis and Polissiou, 1997), and crocusatins -B, -C, -F, -G, -H, -J were isolated and identified from dried stigmas of saffron (Li and Wu, 2002a). Five new monoterpenoids, crocusatins-A, -B, -C, -D, -E, a new lactate, sodium (2*S*)-(*O*-hydroxyphenyl) lactate, and 18 known compounds were isolated and characterized from saffron pollen (Li and Wu, 2002b). From the aqueous extract of the saffron stigmas, four new compounds, crocusatins -F, -G, -H, and -I together with 21 known compounds, were isolated (Li and Wu, 2002a). Montoro et al. (2012) identified crocetin, crocetin derivatives, Crocusatin-B, -C, picrocrocin, safranal, sinapic acid derivative in *C. sativus*

petals. Li and co-workers detected Crocusatins-C, -D, -E, -I, -J, -K, -L in petals (Li et al., 2004).

68.2.3 FLAVONOIDS

In saffron, flavonoids are mainly represented by glycosidic derivatives of kaempferol (Carmona et al., 2006b). Kaempferol 3-O-sophoroside-7-O-β-D-glucopyranoside, sophoraflavonolosid, kaempferol 7-O-β-D-sophoroside were identified abundant in saffron stigmas (Tarantilis and Polissiou, 1997; Straubinger et al., 1997; Moraga et al., 2009a, b). Several kaempferol glycosidic derivatives, namely astragalin (Li et al., 2004; Tung and Shoyama, 2013), populin (Straubinger et al., 1997; Moraga et al., 2009a, b), dihydrokaempferol (García-Rodríguez et al., 2017), dihydrokaempferol 3-O-hexoside (Baba et al., 2015a, b) were isolated from the stigmas. Additionally, quercetin, myricetin (Gismondi et al., 2012), taxifolin 7-O-hexoside, isorhamnetin-3-O-β-D-glucopyranoside (Baba et al., 2015a, b) were also identified.

The major flavonoid constituents identified in saffron petals corresponded to quercetin, kaempferol, naringenin, and kaempferol-3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside (Song, 1990). Around 31 flavonoids comprising mainly glycosidated and metoxilated derivatives of kaempferol, quercetin, isorhamnetin, and tamarixetin were identified in *C. sativus* petal extracts (Montoro et al., 2012) and glycosides as mono-, di- or triglycosides (Goupy et al., 2013). Kaempferol glycosides were the predominant flavonols constituting about 84.0% of total flavonol content, with kaempferol 3-O-sophoroside as the major compound (Montoro et al., 2012; Sánchez-Vioque et al., 2016). Sophoraflavanosid, astragalin (Li et al., 2004; Montoro et al., 2008), populin (Straubinger et al., 1997; Montoro et al., 2008) and quercetin 3,4′-di-O-β-D-glucopyranoside were detected in saffron petals at lower levels (Sánchez-Vioque et al., 2016). Among other flavonoids, dihydrokaempferol, and dihydrokaempferol 3-O-hexoside, quercetin, and its derivatives (Montoro et al., 2008), rhamnetin (Montoro et al., 2012), isorhamnetin, and its derivatives (Nørbæk et al., 2002; Montoro et al., 2008), 7-O-β-D-glucopyranoside of myricetin and apigenin (Nørbæk et al., 2002), isoorientin, vitexin, orientin (Sanchez-Vioque et al., 2016), naringenin (Termentzi and Kokkalou, 2008) and naringenin 7-O-hexoside (Montoro et al., 2008), were detected.

68.2.4 DERIVATIVES OF PHENOLS AND PHENOL CARBOXYLIC ACIDS

Phenolic compounds detected in saffron stigmas include hydrocinnamic acids like methylparaben (Li and Wu, 2002a), caffeic acid, pyrogallol, gallic acid (Karimi et al., 2010; Gismondi et al., 2012), and chlorogenic acid (Gismondi et al., 2012). From the petals, hydroxycinnamic acids namely p-coumaric acid, methylparaben, vanillic acid, protocatechuic acid, p-hydroxybenzoic acid, 3-hydroxy-4-methoxybenzoic acid and a new naturally occurring acid, (3S),4-dihydroxybutyric acid were isolated and identified (Li et al., 2004). Besides, sinapic acid and its derivatives were identified from the saffron petals (Termentzi and Kokkalou, 2008; Monotro et al., 2012). Polysubstituted benzene derivatives, benzoic acid, 4-hydroxybenzoic acid, protocatechuic acid methyl ester and methylparaben were isolated from pollen (Li and Wu, 2002b). Several phenolic compounds namely catechol, vanillin, salicylic acid, cinnamic acid, p-hydroxy benzoic acid, gentisic acid, syringic acid, p-coumaric acid, gallic acid, t-ferulic acid, caffeic acid (Esmaeili et al., 2011) and sinapinic acid (Baba et al., 2015a, b) were detected from saffron corms.

68.2.5 NITROGEN-CONTAINING COMPOUNDS

Nitrogen-containing compounds reported in the stigma of *C. sativus* are vitamin A, vitamin B2, riboflavin, vitamin B6, thiamine, vitamin C, and vitamin E (Khare, 2007; Karimi et al., 2010; Lim, 2014; Hashemi and Erim, 2016). Stigmas and pollen were found to contain adenosine, harman, nicotinamid thymine, tribusterine, and uracil (Li and Wu, 2002a, b). Gao et al. (1999a) isolated adenosine from the plant sprouts.

68.2.6 PHYTOSTEROLS

Ultrasonic-assisted solvent extraction (USE) of saffron from Tibet and China analyzed using gas chromatography-mass spectrometry (GC-MS) detected the presence of stigmasterols and γ-sitosterol (Jia et al., 2011). In *C. sativus* petals, the phytosterols namely, β-sitosterol, stigmasterol, fagasterol, fucosterol were identified (Feizy and Reyhani, 2016). Stigmasterol and β-sitosterol were detected in the plant stigmas (Zheng et al., 2011; Feizy and Reyhani, 2016).

68.2.7 ANTHOCYANIN

Quantification of anthocyanins from *C. sativus* was reported for the first time from the tepals and delphinidin 3,7-O-diglucoside was found to be the major anthocyanin (Goupy et al., 2013). Lotfi et al. (2015) identified the anthocyanins, delphinidin 3-O-β-D-glycopyranoside, petunidin, pelargonidin 3-O-β-D-glycopyranoside, pelargonidin 3,5-glycosides, 3,5 cyanidin-diglycosides in saffron tepals by HPLC analysis. Monomeric anthocyanins in saffron petal extracts were quantified by Khazaei et al. in 2016.

68.2.8 TRITERPENOID SAPONINS

Rubio-Moraga et al. (2011) isolated a mixture of highly glycosylated triterpenoid saponins was isolated from *Crocus sativus* corms. The mixture contained two new oleanane-type saponins, the isomers Azafrine 1 and Azafrine 2, with different configurations of three substituents.

68.2.9 ACETOPHENONES AND ANTHRAQUINONES

In 1999, Gao et al. isolated two new acetophenone derivatives, 2,4-dihydroxy-6-methoxyacetophenone-2β-D-glucopyranoside, 2,3,4-trihydroxy-6-methoxyacetopenone-3-β-D-glucopyranoside, a new γ-lactone glucoside, and 3-(*S*)-3-β-D-glucopyranosyloxybutanolide from the sprouts of *Crocus sativus* (Gao et al., 1999a). Later they isolated and identified two novel anthraquinones, 1-methyl-3-methoxy-8-hydroxyanthraquinone-2-carboxylic acid and 1-methyl-3-methoxy-6,8-dihydroxyanthraquinone-2-carboxylic acid and two known anthraquinones emodin, 2-hydroxyemodin from the sprouts (Gao et al., 1999b).

68.2.10 OTHER IMPORTANT PHYTOCHEMICALS FROM VARIOUS PARTS OF C. SATIVUS

68.2.10.1 Stigmas

Amino acids, namely alanine, proline, and aspartic acid, have been detected in high level from saffron samples originated from different countries (Del Campo et al., 2009). Myristic acid, stearic acid and palmitic acid, are reported to be the main saturated fatty acids along with some unsaturated fatty acids like palmitoleic, oleic, gadoleic acid, linoleic, linolenic, and arachidonic acid docosapentaenoic acid (USDA, 2013; Lim, 2014).

68.2.10.2 Petals and Pollen

According to Feizy and Reyhani (2016), linoleic acid, linolenic acid and palmitic acid are the most abundant fatty acids in *C. sativus* petals. The ether fractions of *C. sativus* petals, stamens, and stigmas analyzed by GC-MS revealed the presence of hexadecanoic acid, 4-hydroxydihydro-2(3H)-furanone, lauric acid and stigmasterol as the common constituents (Zheng et al., 2011). Protein, fat, ash, fiber, sodium, potassium, calcium, copper, iron, magnesium, zinc, and phosphorus were reported to be among the active ingredients in saffron petal (Fahim et al., 2012). In 2013, Serrano-Diaz et al. found that the whole flowers of saffron have high ash, protein, and available carbohydrates and are low in lipids. According to them, stamens are the flower part with the highest content of protein, ash, and lipids. Li and Wu (2002b) isolated and characterized a new lactate from saffron pollen.

68.2.10.3 Leaves

Predominant accumulation of protein, lipids, total carbohydrates, sodium, and nitrogen was observed in the proximate and mineral analysis of the leaves (Jadouali et al., 2018).

68.2.10.4 Corms

A novel glycoconjugate was isolated from the saffron corms, of which the polysaccharide part dominated by rhamnose constitute the majority of the molecule and asparagine/aspartic acid, alanine, glutamic acid/glutamine, glycine, and serine are the main protein constituents (Escribano et al., 1999). Hexadecanoic acid and octadecadienoic acid were the major constituents among the volatile compounds detected from the petroleum ether extract of *C. sativus* corms (Yu-Zhu et al., 2008).

68.3 MAJOR PHARMACOLOGICAL PROPERTIES

68.3.1 ANTIOXIDANT ACTIVITY

Crocetin, crocin, safranal, and phenolic compounds from *C. sativus* stigmas exhibit potent intracellular free radical scavenging activity and protect cells and tissues against oxidation (Hu et al., 2015). Moreover, much attention is paid to various by-products of *C. sativus*, namely perianth, leaves, green

leaves, corms, tunics, spathes, and stamens (Montoro et al., 2012; Smolskaite et al., 2011; Lahmass et al., 2018). The results showed that all extracts exhibit antioxidant and free radical scavenging properties.

68.3.2 ANTIHYPERTENSIVE ACTIVITY

The aqueous and ethanolic extracts (EEs) of *C. sativus* petals showed a reduction in blood pressure in a dose-dependent manner (Fatehi et al., 2003). The ethanol extract induced greater changes in EFS in the rat isolated vas deferens and guinea-pig ileum than the aqueous extract (Fatehi et al., 2003).

68.3.3 ANTICONVULSANT ACTIVITY

Hosseinzadeh and Khosravan (2002) evaluate the anticonvulsant activity of *C. sativus* stigma and the constituents safranal and crocin in mice using the PTZ-induced convulsions. Safranal reduced the seizure duration, delayed the onset of tonic convulsions, and protected the mice from death which showed anticonvulsant activity. Crocin did not show any anticonvulsant activity (Hosseinzadeh and Talebzadeh, 2005). Safranal is a strong and effective anticonvulsant and also an agonist at GABAA receptors, and the nose-to-brain delivery via nanoparticle formulation improved its brain delivery (Pathan et al., 2010).

68.3.4 ANTITUSSIVE ACTIVITY

The EE of *C. sativus* (100–800 mg/kg) and safranal (0.25–0.75 ml/kg) showed antitussive activity with reduced number of coughs. The alcoholic and water extracts (WEs) of petal and crocin did not show antitussive activity (Hosseinzadeh and Younesi, 2002).

68.3.5 ANTINOCICEPTIVE AND ANTI-INFLAMMATORY EFFECTS

Stigma and petal extracts of saffron exhibited antinociceptive or nociception effects in chemically induced pain test as well as acute or chronic anti-inflammatory activity, and these effects may be due to the presence of flavonoids, tannins, anthocyanins, alkaloids, and saponins (Hosseinzadeh and Younesi, 2002).

68.3.6 ANTIGENOTOXIC AND CYTOTOXIC EFFECTS OF SAFFRON

The antigenotoxic and cytotoxic effects of *C. sativus* were studied using the Ames/Salmonella test system. The two well-known mutagens (BP, 2AA), the colony-forming assay and four different cultured human normal cell line (CCD-18LU) and malignant cell line (Hela, a-204 and Hepg2) cells are used. When we are using only the TA98 strain in the Ames/Salmonella test system, saffron showed non-mutagenic activity, as well as non-anti-mutagenic activity against BP-induced mutagenicity and demonstrated a dose-dependent co-mutagenic effect on 2-AA-induced anti-mutagenicity. Safranal, the saffron component was majorly responsible for this unusual co-mutagenic effect (Abdullaev, 2003).

68.3.7 EFFECT ON SEXUAL BEHAVIOR

The study by Hosseinzadeh et al. (2008) exhibited an aphrodisiac activity of saffron aqueous extract and its constituent crocin. Safranal did not show aphrodisiac effects.

68.3.8 ANTI-ALZHEIMER'S EFFECT

The main carotenoid constituent in this plant which is trans-crocin-4, the digentibiosyl ester of crocetin, inhibited A-beta fibrillogenesis which is formed by the oxidation of the amyloid beta-peptide fibrils in Alzheimer's disease.

The aqueous methanolic (50:50, v/v) extract of *C. sativus* stigmas inhibited A-beta fibrillogenesis in a concentration dependent and time-dependent manner at lower concentrations than it's another constituent dimethylcrocetin (Zarghami and Heinz, 1971).

68.3.9 CARDIO PROTECTION

Crocetin which is the main active component of saffron was found to decrease the level of the cardiac marker - lactate dehydrogenase and its activity, also increases the mitochondrion potential in a cardiac myocytetreated with which is nor adrenaline, suggesting its cardio protective action (Premkumar et al.,

2001). Saffron also shown to possess calcium antagonistic activity. This antagonistic activity was through the blockage of extracellular $Ca^{(2+)}$ influx through receptor-operated $Ca^{(2+)}$ channels and potential dependent $Ca^{(2+)}$ channels (Abe and Saito, 2000). In another study, crocetin prevented the cardiac hypertrophy, which is induced by norepinephrine by increasing the levels of the antioxidant enzymes, namely myocardial superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) peroxidase and also significantly improved the myocardial pathological and histological changes which were induced by norepinephrine (Shen et al., 2004).

68.4 CONCLUSION

In the present review, we attempted to summarize the important chemical profile and pharmacological activities reported in various parts of the commercially valuable plant *C. sativus.* The plant comprises many valuable, therapeutically promising compounds, which include carotenoids, flavonoids, hydroxycinnamic acids, anthocyanins, terpenoids, etc. In the wide range of pharmacological activities of isolated compounds, antioxidant, antitumor, antihypertensive, and cardioprotection have special therapeutic value. Many biologically active compounds reported from the plant remain unresearched, and further isolation of and research into pharmacological activities of the species seem a promising direction in the search for new drugs with a wide spectrum of activity.

KEYWORDS

- ***Crocus sativus***
- **gas chromatography-mass spectrometry**
- **monoterpenoids**
- **phytosterols**
- **triterpenoid saponins**
- **ultrasonic-assisted solvent extraction**

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CHAPTER 69

Phytochemical and Pharmacological Profile of *Dendrobium aphyllum* (Roxb.) Fischer

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69.1 INTRODUCTION

Dendrobium is one of the largest diverse genera of orchids and comprises about 1,600 species. The genus is very popular throughout the world, for the magnificent flowers of great delicacy and beauty. This genus exhibits great variations in the external morphology, for example, size, habit, form of stem, leaf, shape, and color of flowers. The generic name *Dendrobium* means living on a tree. The plants of this genus have more than one stem; some are pseudobulbous, few with jointed cane like stems and others in variety of forms and size. The leaves are strap-shaped or ovate, or sometimes very narrow and grass-like; they are either deciduous or persistent till the pseudobulbs perish. The flowers are borne on lateral or terminal branches from the nodes of the pseudobulbs or in the apical clusters or spikes. The seed capsule is oval, oblong, or ovoid. The genus *Dendrobium* is distributed in India, Myanmar, Bangladesh, Malaysia, Australia, New Zealand, Nepal, China, Japan, and Thailand.

Dendrobium aphyllum (Roxb.) Fischer is distributed in India, Myanmar, Bangladesh, Thailand, Indochina, W. China, Malaya, and Nepal. It is an attractive epiphyte orchid. Stems are long (90–100 cm), compressed, decumbent, subclavate, and leafy throughout. Leaves are 10–15 cm long and 4 cm broad, ovate-lanceolate, and acuminate. Flowers 2–3, on a short peduncle

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from the node, 3 cm long, pale rose, lip yellow; sepals' oblong-lanceolate, subacute; petals broader and oblong. Lip orbicular, pubescent, and ciliate, base tubular by the incurving sides. It is leafless at the time of flowering. It comes to the flowering during March-May (Hegde, 1984).

69.2 PHYTOCHEMISTRY AND HERBAL USAGE

Phytochemical studies on leaves of *D. aphyllum* revealed the presence of alkaloids, glycosides, flavonoids, saponins, tannins, terpenoids, steroids, quinine, and coumarin (Akter et al., 2018). Further, preliminary phytochemical studies of leaves and pseudobulbs (stem) revealed the presence of α-amino acid, carbohydrates, reducing sugar, glycoside, terpenoids, and steroids (Khing and Thant, 2019).

Chen et al. (2008) isolated compounds such as flavanthrin (Figure 69.1(A)), coelonin (Figure 69.1(B)), lusianthridin (Figure 69.1(C)), moscatin (Figure 69.2(D)), gigantol (Figure 69.1(E)), batatasin III (Figure 69.1(F)), dibutyl phthalate (Figure 69.1(G)), diisobutyl phthalate (Figure 69.1(H)) and p-hydroxyphenylpropionic methyl ester (Figure 69.1(I)), respectively from dried powdered whole plant ethanol (95%) extract of *D. aphyllum.*

Shao et al. (2008) isolated eight compounds and identified as 4′-methoxyl-tricin, tricin, 7,3′,5′-tri-O-methyl-tricetin, syringic acid, (+)-syring-aresinol, D-allitol, sucrose, and icariside D2 from *D. aphyllum* extracts. Compounds such as 4′-methoxyl-tricin, tricin, 7,3′,5′-tri-O-methyl-tricetin, D-allitol, sucrose, and icariside D2 were isolated for the first-time in genus *Dendrobium*.

Zhang et al. (2008) isolated compounds such as moscatilin, gigantol, batatasin, tristin, 3,5,4′-trihydroxylbibenzyl, 3,5-dimethoxyl-4, 4′-dihydroxylbibenzyl, moscatin, 2,4,7-trihydroxyl-9, 10-dihydrophenanthrene, hircinol, 2-(4-hydroxyphenyl) ethyl-beta-D-glucopyranoside, salidroside, and p-hydroxylbenzylacetic acid. Compounds salidroside and p-hydroxylbenzylacetic acid were isolated in this genus for the first time.

Yang et al. (2015) isolated 14 phenolic compounds, including one new phenanthrone, aphyllone A (Figure 69.2(A)) and four new bibenzyl derivatives, aphyllone B (Figure 69.2(B)) and aphyllal C, aphyllal D and aphyllal E (Figure 69.2(C–E)) together with nine known compounds moscatin, hircinol, moscatilin, gigantol, batatasin III, tristin, dihydroresveratrol, trigonopol B and tricetin 3′,4′,5′-trimethyl ether 7-Oβ-glucopyranoside from the ethanol stem extract of *D. aphyllum*.

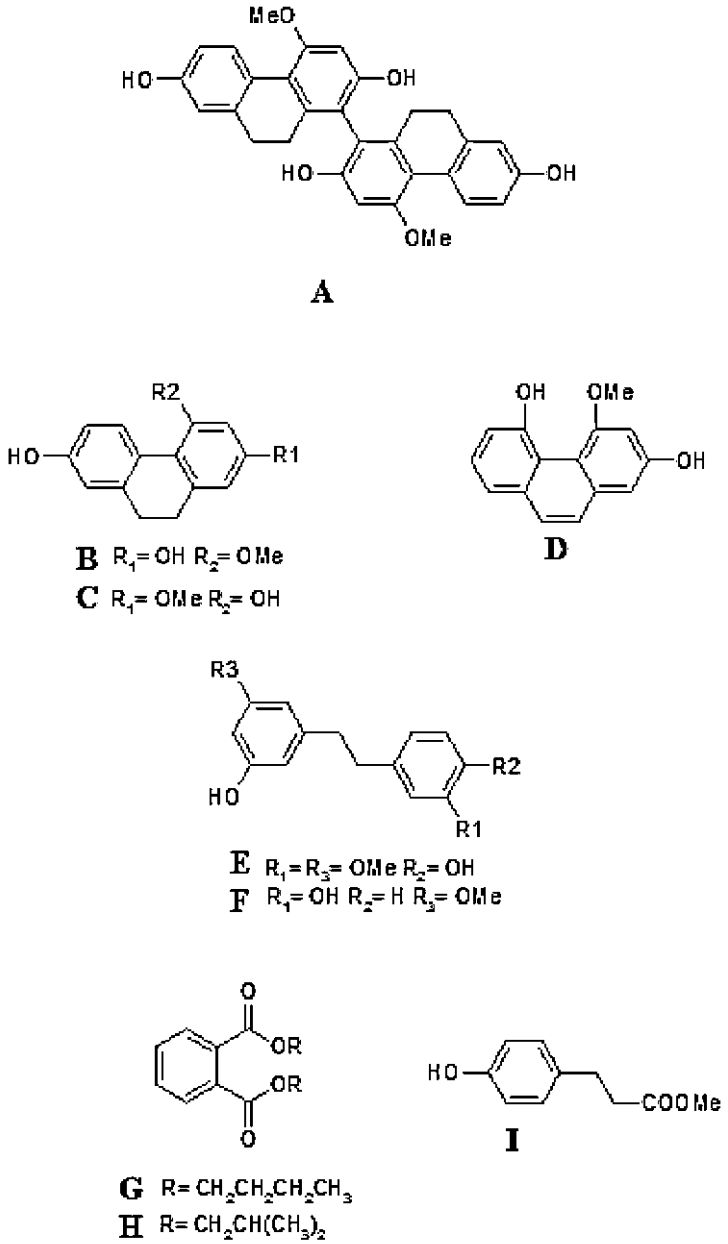


FIGURE 69.1 (A) Flavanthrin; (B) coelonin; (C) lusianthridin; (D) moscatin; (E) gigantol; (F) batatasin III; (G) dibutyl phthalate; (H) di-isobutyl phthalate; and (I) p-hydroxyphenylpropionic methyl ester.

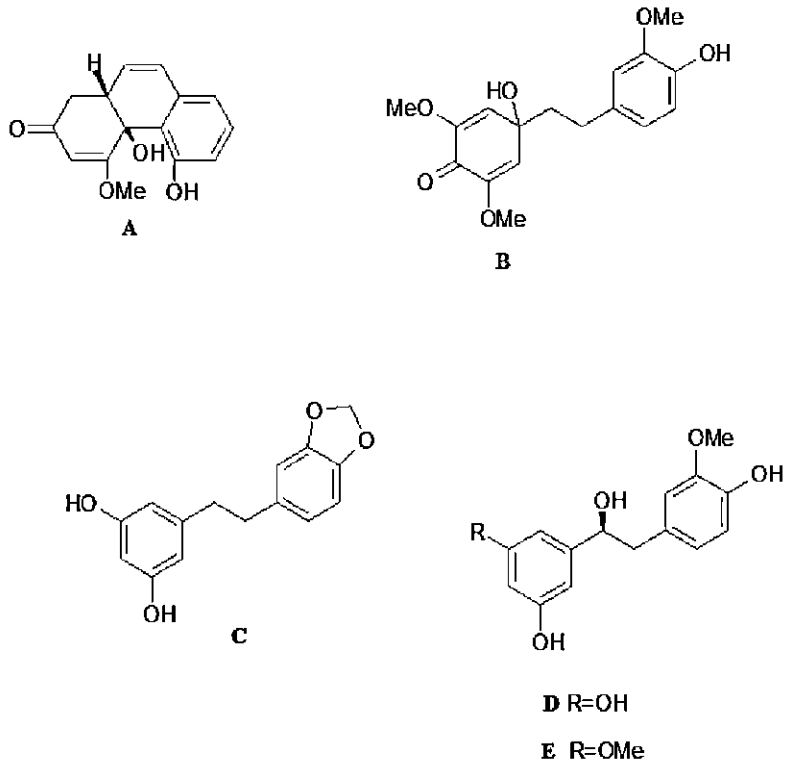


FIGURE 69.2 (A) Aphyllone A; (B) aphyllone B; (C) aphyllal C; (D) aphyllal D; and (E) aphyllal E.

Stems are used to prepare a tonic in Nepal (Pant and Raskoti, 2013). Eardrops prepared with juice of young pseudobulbs of this plant are used by the Valmikis tribe of Visakhapatnam, India to treat ear-problems (Reddy et al., 2005). Leaf paste is used for deformed head structure in newly born children, applied on the abnormal or deformed parts of the head of newly born baby to get normal shape (Huda et al., 2006; Hossain, 2009). Leaves are used in the treatment of wounds, earache, epilepsy, paralysis (Akhter et al., 2017). Juice of leaf is also used to treat skin disorders (Rahamtulla et al., 2020a). Stem is used as a tonic. Whole plant is used for abdominal pain, body ache, carve-depression, eye inflammation, blear, diabetes, heavy menstruation, rheumatism, and leucorrhea (Akhter et al., 2017). The paste of whole plant is applied to boils (Rahamtulla et al., 2020a) and snake bites (Rahamtulla et al., 2020b).

69.3 PHARMACOLOGY

69.3.1 ANTIOXIDANT ACTIVITY

Yang et al. (2015) carried out DPPH radical scavenging activities on compounds such as aphyllone A, aphyllone B and aphyllal C isolated from *D. aphyllum* stem extract at the concentration of 100 μg/mL. Among the compounds tested aphyllone B displayed significant scavenging percentage (87.97%). Compounds aphyllone A and aphyllal C exhibited moderate activities, i.e., 5.25% and 35.28%.

Bhattacharyya et al. (2018) carried out the comparative assessment of antioxidant activity of various plant parts of *D. aphyllum* (mother plant and micropropagated) using DPPH and FRAP antioxidant assays using different plant extracts. Their studies revealed that highest antioxidant activity was exhibited by the methanolic leaf extract of the micropropagated plants and lowest in the chloroform extracts (CEs).

69.3.2 ANTI-INFLAMMATORY ACTIVITY

Phenolic compounds from *D. aphyllum*, namely moscatin, moscatilin, and tricetin 3′,4′,5′-trimethyl ether 7-O--glucopyranoside, inhibited NO production at the concentration of 25 μM in LPS-stimulated RAW 264.7 cells with the inhibition of 32.48%, 35.68%, and 38.50%, respectively (Yang et al., 2015).

Anti-inflammatory activity of alkaloids isolated from *D. aphyllum* on LPS-induced RAW 264.7 macrophages was carried out by Wang et al. (2020). These studies conclude that *D. aphyllum* alkaloid treatment inhibited LPS-induced NO production and decreased IL-1, IL-6, TNF-a, and PGE2 secretion in the RAW 264.7 macrophages.

69.3.3 IMMUNOMODULATORY ACTIVITY

Liu et al. (2017) used crude polysaccharide extract from the stem of *D. aphyllum* for immunological effects, including cytokine secretion levels as well as pinocytic and phagocytic capacities, in the macrophage cell line RAW 264.7. Liu et al. (2017) noticed that *D. aphyllum* polysaccharide (DAP) treatment enhanced cytokine secretion (nitric oxide (NO), interleukin-6 and tumor necrosis factor-a) and pinocytic and phagocytic capacities of RAW 264.7 mouse macrophages. The complement receptor 3 and mannose receptor were identified to be the receptors of DAP on RAW 264.7 cells,

indicating that the Akt/mTOR/MAPK and IKK/nuclear factor-KB pathways could be involved in DAP-activated immunomodulation.

A previous study of an edible DAP by Liu et al. (2017) characterized the structure-associated immunomodulatory effects and the *in vitro* gastrointestinal digestions highlighted DAP could be digested by the GI tract in some extent.

Liu et al. (2019) further explored the digestive properties *in vivo* to infer the metabolic pathway with health mice model. Their results revealed that DAP-treated group showed slightly lower blood glucose levels and significantly higher enzyme activities, namely G6Pase and GDH with an increment of about 0.4 to 0.9 and 45 to 91 U/mL, respectively. Meanwhile, DAP up regulated the expression of glucose transporters, GLUT1 and GLUT2 in the increment rates of 56.34% to 68.28% and 76.63% to 83.03%, in colon. Furthermore, they described the possible metabolic pathway of a novel bioactive polysaccharide extracted from *D. aphyllum*.

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KEYWORDS

- **anti-inflammatory**
- ***Dendrobium aphyllum***
- **glucose transporters**
- **immunomodulatory activity**
- **macrophage cell line**
- **metabolic pathway**

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CHAPTER 70

Bioactives and Pharmacology of Stinking Cassia: *Senna tora* (L.) Roxb. (Syn. *Cassia tora* L.)

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70.1 INTRODUCTION

Senna tora (L.) Roxb. (Syn.: *Cassia tora* L.) is a small annual herb or under shrub, belonging to the family Fabaceae that grows as a common weed in many Asian countries, including central and southern India, Korea, Nepal, Nigeria, and China (Farah et al., 2011). It is commonly called Charota in Hindi, Chakunda in Punjabi, Chakramardah in sanskrit, Tagarai in Tamil, Takara in Malayalam, Taragasi in Karnataka, Tankli or Takla in Marathi and Tantemu in Telugu. It is found throughout India, mainly in Himachal Pradesh, Bihar, and Orissa, and it constitutes an ayurvedic preparation 'Dadhughnavati' – a widely used antifungal formulation. This herb is usually 1–1.2 m in height, has compound paripinnate leaves and bright, yellow-colored flowers. Pods are long, slender, and obliquely separate and seeds are green and rhombohedral (Sharma et al., 2005). The seeds of *S. tora*, also known as Juemingzi in Chinese, are used as popular traditional Chinese medicine and are mentioned in the Chinese pharmacopeia as well (Uttam et al., 2009). The seeds are used for various eye diseases, liver complaints and boils all throughout China (Das et al., 2011). In Ayurveda, it is often used as a laxative, antiperiodic, and is also proven effective against leprosy, skin diseases, ringworm, bronchitis, cardiac disorders, ophthalmic, hepatic disorders, and various hemorrhoids (Niranjan et al., 2010).

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70.2 BIOACTIVES

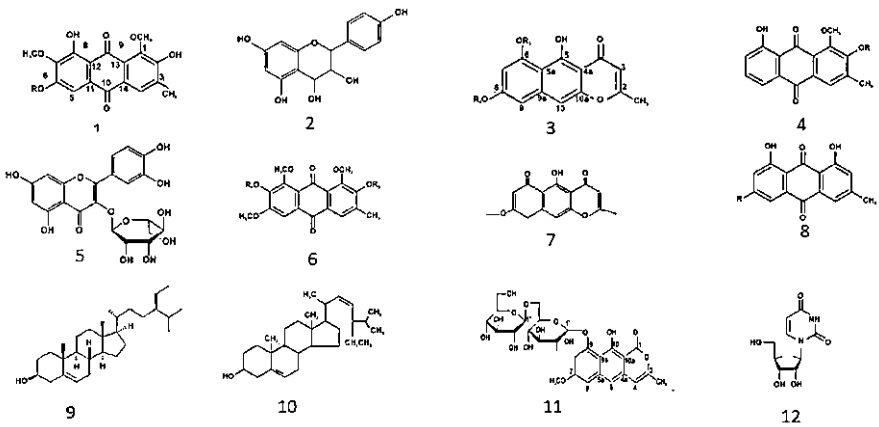
The bioactive constituents present in *Senna tora* are anthraquinones, including 1-desmethylchryso-obtusin, aurantio-obtusin, 1-desmethylaurantion-obtusin, chryso-obtusin, obtusin, etc. (Wu and Yen, 2004). Five anthraquinones like chryso-obtusin, obtusin, aurantio-obtusin, 1-desmethylaurantio-obtusin, and 1-desmethylchryso-obtusin were isolated and purified by high-speed counter-current chromatography and semi-preparative high-performance liquid chromatography from *S. tora* (Yu et al., 2008). The plant shows the presence of chrysophanol as a marker constituent (Evans, 1996).

S. tora gum is obtained from the seeds of *Senna tora*. Methylation studies proved that polysaccharide consists of 1, 4 linked D-mannopyranose and D-glucopyranose units. It is one of the cheapest gums available in India, however, it has a few drawbacks such as very low solubility in water (cold water 22.8%, hot water (80°C) 50.8% and water insoluble 27.93%), dull color of gum solution and fast biodegradability (Soni and Pal, 1996). An anthraquinone glucoside was isolated from the seed extract and characterized as alaternin 2-O-α-D glucopyranoside (Lee et al., 1998). The seed oil contains different percentages of mixed fatty acids including palmitic, stearic, lignoceric, oleic, and linoleic acid (Farah et al., 2011).

Three naphthopyrone glucosides called cassiaside, rubrofusarin-6-O-ß-D-gentiobioside, and toralactone-9-O-ß-D-gentiobioside, were isolated from the Butanolic-soluble seed extract of *Senna tora*, by using an *in-vitro* bioassay which is based on the inhibition of advanced glycation end products (AGEs) (Lee et al., 2006). From the roasted seeds of *Cassia tora*, a new naphthopyrone glycoside was isolated and characterized as 10-[(ß-D-glucopyranosyl-(1>6)-O-ß-D-glucopyranosyl)oxy]-5-hydroxy-8-methoxy-2-methyl-4H-l-naphtho[1,2-b]pyran-4-one (isorubrofusarin gentiobioside). Isorubrofusarin gentiobioside, alaternin, and adenosine were also isolated and identified (Lee et al., 1997). The effect of temperature on the chemical constitution of seeds was examined. As the temperature was gradually raised, the level of free chrysophanol increased (Farah et al., 2011).

The root extract also showed the presence of 1,3,5-trihydroxy-6-7-dimethoxy-2-methyl anthraquinone and beta-sitosterol. Ononitol monohydrate, which is similar in structure to glycosides was isolated from *Senna tora* leaves (Ignacimuthu et al., 2009). The leaves also contain emodin, tricontan-1-ol, stigmasterol, freindlen, beta-sitosterol, beta-D-glucoside, stearic, succinic, palmitic, and d-tartaric acids, uridine, quercitrin, and iso-quercitrin

(Shibata et al., 1969). *S. tora* flowers are found to contain kaempferol and leucopelargonidin (Farah et al., 2011).



(1) R=H Aurantio-obtusin
R=CH_3 Chryso-obtusin

(2) Kaempferol

(3) Leucopelargonidin
R_1= Glucosyl, R_2=H Cassiaside
R_1= Gentiobiosy, R_2=CH_3 Rubrofusarin-6-O-β-gentiobioside

(4) Quercitrin

(5) R=H Obtusifolin
R=glc Obtusifolin-2-β-D-glucoside

(6) R_1=R_2=H Obtusin-2-O-β-D-glucoside
R_1=H, R_2=glc Obtusin

(7) Rubrofusarin

(8) R=OCH_3 Physcion
R=OH Emodin
R=H Chrysophanol

(9) β sitosterol

(10) Stigmasterol

(11) Toralactone-9-O-β-D-gentibioside

(12) Uridine

70.3 PHARMACOLOGY

70.3.1 CYTOTOXIC ACTIVITY

Anthraquinones aglycons from *S. tora* are said to show inhibitory effect against aflatoxin B1 (AFB1) in the Ames test. Several reports suggest these can act as an antimutagens and suppress the mutagenicity of mycotoxins and polycyclic aromatic hydrocarbons (Hao et al., 1995).

70.3.2 HYPOLIPIDEMIC ACTIVITY

Ethanolic extract of seeds of *S. tora,* and its different fractions were investigated for hypolipidemic activity on trition-induced hyper-lipidemic profile. Ethanolic extract (EE) and its ether soluble and water-soluble fraction decreased serum level of total cholesterol (TC), increased the serum HDL-cholesterol, decreased triglyceride level, also reduced LDL-cholesterol levels (Patil et al., 2004).

70.3.3 ANTI-INFLAMMATORY ACTIVITY

Methanolic extract of *S. tora* leaves was evaluated for the anti-inflammatory effect against carrageenan, serotonin, histamine, and dextran-induced hind paw edema in rats. The extract was found to show maximum inhibition of edema of 40.33%, 31.37%, 53.57%, and 29.15% at the end of 3 hours with carrageenan, dextran, histamine, and serotonin-induced rat paw edema, respectively (Maity et al., 1998).

70.3.4 ANTINOCICEPTIVE ACTIVITY

Methanolic extract of leaves of *S. tora* was investigated for the spasmogenic effect on guinea pig ileum, rabbit jejunum, and mice intestinal transit. The extract was found to contract smooth muscles in a concentration-dependent manner. The extract also increased intestinal transit in mice dose-dependently (Chidume et al., 2002).

70.3.5 ANTI-SHIGELLOSIS ACTIVITY

The root of *S. tora* exhibited anti-shigellosis activity. The ethyl acetate (EAE) fraction of the root extract showed maximum activity with the zone of inhibition ranging between 23 and 25 mm at the concentration of 200 µg per disc (Awal et al., 2004).

70.3.6 ESTROGENIC ACTIVITY

Two new phenolic triglycosides alongside seven known compounds were isolated through a bioassay-guided fractionation of 70% EE of *S. tora* seeds (El-Halawany et al., 2007). The estrogenic effect of the fractions exhibited by the EE and its isolated compounds were investigated using estrogen dependent proliferation of MCF-7 cells. A basic nucleus 1,3,8-trihydroxynaphthalene was found to play a key role in influencing the binding affinity of these compounds to estrogenic receptors. *S. tora* leaves extract showed maximum antifertility activity in female rats. The antifertility activity of the drug has been found to be related to estrogenic activity (Sinha et al., 1999).

70.3.7 ANTIOXIDANT ACTIVITY

The methanol and aqueous extract of the dried aerial parts of *S. tora* were checked for their potential antioxidant activity. Methanolic extract showed strong antioxidant activity as compared to aqueous extract (Uddin et al., 2008).

70.3.8 ANTIMICROBIAL ACTIVITY

Antifungal activity of the dealcoholized extract of leaves of *S. tora* was demonstrated on five different fungal organisms; *Candida albicans, Aspergillus niger, Saccharomyces cerevisiae, Trichophyton mentagrophytes* when tested through turbidity and spore germination methods in a concentration dependent manner (Mukherjee et al., 2009). Methanolic extracts (1 mg/ml conc.) prepared from leaves of *S. tora* showed antifungal activity against *Microsporum gypseum, Trichophyton rubrum* and *Penicillium marneffei* (Souwalak et al., 2004). Crude methanolic extracts prepared from leaves of *S. tora*, showed distinct zones of inhibition against *Candida albicans* (cup-plate method) along with MIC of 2 mg/ml with the same extract (Pawar et al., 2011). A major antifungal compound, chrysophanic acid-9-anthrone was isolated and identified from *C. tora* seed powder and it was active against *Trichophyton rubrum, T. mentagrophytes, Microsporum canis, M. gypseum* and *Geotrichum candidum* in broth medium with 100 µg/ml L-ascorbic acid as antioxidant (Acharya and Chatterjee, 1975). A few phyto-pathogenic fungi like *Botrytis cineria*, *Erysiphe graminis*, *Phytophthora infestans*, and *Rhizoctonia solani* also showed susceptibility against methanolic extract from

seeds of *S. tora*. Whereas no activity was seen against *Puccinia recondita*, *Pyricularia grisea* (Kim et al., 2004). Aqueous extract of *S. tora* leaves and seeds showed potent activity against both gram-positive and gram-negative organisms except *Bacillus* subtilis (Patel and Patel, 1957).

70.3.9 ANTI-HELMINTHIC ACTIVITY

Alcoholic and aqueous extracts from the seeds of *S. tora* were checked for their anti-helminthic activity against the organisms; *Pheretima posthuma* and *Ascardia galli*. Both the extracts exhibited significant antihelminthic activity at the highest concentration of 100 mg/ml (Deore et al., 2009).

70.3.10 HEPATOPROTECTIVE ACTIVITY

Hepatoprotective efficacy of ononitol monohydrate, isolated from *S. tora* leaves was observed on CCl_4 induced hepatotoxicity in male rats. *In-vivo* study showed decreased levels of serum transaminase, lipid peroxidation (LPO) and TNF-α, but showed increased levels of antioxidants and hepatic glutathione (GSH) enzyme activities. In comparison to the reference drug Silymarin, ononitol monohydrate showed higher hepatoprotective activity (Ignacimuthu et al., 2009).

70.3.11 LARVICIDAL ACTIVITY

Methanolic extract of *S. tora* seeds was examined against 4th stage larvae of *Aedes aegyptii* and *Culex pipiens pallens*. More than 90% mortality was observed at 200 ppm and was significantly reduced at lower dosage concentrations (Jang et al., 2002).

70.3.12 ANTIMUTAGENIC ACTIVITY

Methanolic extract of *S. tora* seeds were evaluated against AFB1 for antimutagenic activity with the help of *Salmonella typhimurium* assay. The population of revertants per plate decreased to a significant extent when this extract was added to the assay system. Later, it was found that the CH_2Cl_2 and n-BuOH fractions of the methanolic extract possessed antimutagenic activity, but the aqueous fraction was inactive (Choi et al., 1997).

70.3.13 HYPOTENSIVE EFFECT

Seeds of *S. tora* elicit hypotensive effects in anesthetized rats. Results indicate the effect possibly involves a vagal reflex which reciprocally alters the vasomotor tone of the centrally emanating sympathetic nervous system. It is shown that the capacity of the extract to reduce blood pressure is significantly lesser in vagotomized rats and that hypotensive effects are greatly antagonized in rats whose sympathetic nervous systems are interrupted by transaction of the spinal cord (Koo et al., 1976a). Methanolic extract of the *S. tora* seeds (250 mg/kg, i.v.), prepared using Soxhlet, exhibited hypotension and bradycardia effects on Sprague–Dawley rats (Koo et al., 1976b). The raw seed extract of seeds of *S. tora* showed potential in having Angiotensin Converting enzyme (ACE) inhibitory activity but were significantly less than the standard Captopril (Hyun et al., 2009).

70.3.14 WOUND HEALING ACTIVITY

Methanolic extract of leaves of *S. tora* in an ointment was tested for its wound healing activity by excision wound model and incision wound model, and was found to be comparable with the standard drug povidone-iodine (Janghel et al., 2012).

70.3.15 ANTIDIABETIC ACTIVITY

Kumar et al. (2016) found that the seed extract of *S. tora* is a better drug as a natural product to regress diabetic dyslipidemia and oxidative stress in diabetes. Emodin and Rhein present in EEs of *S. tora* seeds prevented mitochondrial dysfunction and diabetic retinopathy (Ko et al., 2021).

70.3.16 PURGATIVE ACTIVITY

Around 90% of methanolic extracts prepared from dried leaves of *S. tora* showed a purgative effect along with isolated aloe-emodin comparable to standard purgative Sennoside (Maity et al., 2003).

70.3.17 ANTI-PSORIATIC ACTIVITY

Ethanolic extract of *S. tora* leaves exhibits a significant anti-psoriatic activity. It decreased the relative epidermal thickness of the skin in animal

models. The study carried out by Vijayalaxmi et al. (2014) indicated that *S. tora* leaves and the flavonoids isolated from them can be used as natural therapeutic drugs to prevent psoriatic complications.

KEYWORDS

- **angiotensin-converting enzyme**
- **anthraquinones**
- **bioactives**
- ***Cassia tora***
- **hypolipidemic activity**
- ***Senna tora***

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CHAPTER 71

Phytochemistry and Immense Medicinal Properties of *Syzygium alternifolium* (Wight) Walp.

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71.1 INTRODUCTION

Syzygium alternifolium (Wight) Walp. belongs to the family Myrtaceae, which is native to Kadapa, Kurnool, Chittoor districts, and north Arcot district in South India (Balfour, 1869, 1870). *S. alternifolium* is a semi-evergreen mass flowering tree species that grows especially in dry deciduous forests. A synonym of this plant is *Eugenia alternifolia* Wight (WCSP, 2012). Leaf shedding is partial during January-March, and flowering appears in April and May. The fruits of *S. alternifolium* exhibit different colors like green, light purple, dark purple, and violet during growing and maturing. Fruit is like a globose berry with 25–30 mm in diameter and is fleshy and luscious. The taste of the fruits is somewhat sweet and mildly sour with astringent flavor and colors the tongue purple when eaten. The green and light purple fruits are very sweet and tasty whereas, dark purple and violet fruits are bitter and sweet. Fruits are fallen off during late July and August. The local people collect the fallen fruits from the ground and ripen fruits from the tree since they are edible and have commercial value. Each fruit of the plant produces a single large seed.

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Different parts of the *S. alternifolium* have so many medicinal activities. The leaves are used in the treatment of liver cirrhosis, hepatitis, jaundice, and other ailments of the liver and gall bladder. Leaves are also used as curry to treat dry cough by frying them in cow ghee. The tops of the plants are used to treat skin diseases as it has significant anti-fungal properties (Reddy et al., 1989). The mixture of mineral oil and leaves of *S. alternifolium* is used for the darkening of the hair and to promote hair growth by applying to the scalp. Tender shoots, leaves, and fruit juices are used to treat dysentery, seeds are used for diabetes and stem bark is used for gastric ulcers (Reddy et al., 1989; Nagaraju and Rao, 1990; Kameswara Rao and Appa Rao, 2001).

71.2 BIOACTIVES

Phytochemical screening of stem and fruit extracts revealed the presence of alkaloids, flavonoids, carbohydrates, steroids, saponins, indoles, leucoanthocyanins, and proteins (Sudhakar et al., 2012). Phenolic compounds and cinnamic acid are the bioactive principles present in the aqueous extracts of seeds of *S. alternifolium* (Kasetti et al., 2012). Preliminary phytochemical screening of leaves has revealed the presence of flavonoids, tannins, and phenols (Priyadarsini et al., 2016). Detailed phytochemical analysis of *S. alternifolium* leaf extracts reported the presence of flavonoid compounds eucalyptin and tefrowastin and terpenoids (Freidelin) (Pulla Reddy et al., 2005). Rao et al. (2015) reported the presence of a new pentacyclic triterpenoid, 3 β-O-(E)-caffeoyl methyl oleanolate along with the three known flavonoids, 5-hydroxy-7,4′-dimethoxy-6,8-di-C-methylflavone, kaempf-3-O-β-D-glucopyranoside and kaempferol-3-O-α-L-rhamnopyranoside in fruits of *S. alternifolium*.

71.3 PHARMACOLOGY

71.3.1 ANTIOXIDANT ACTIVITY

Hydroxyl radical is the most reactive among reactive oxygen species (ROS), which induces severe damage to adjacent biomolecules. The *S. alternifolium* seed aqueous extract also possesses potent hydroxyl radical scavenging activity. The activity was in a concentration dependent manner of the extract as well as standard BHT. The extract had shown maximum (95%) activity compared to the BHT at the concentration of 100 µg/ml (Ramesh et al., 2009).

Maximum (93%) free radical (DPPH) scavenging activity was observed at the concentration 250 µg/ml of the *S. alternifolium* seed aqueous extract and it was greater than that (67%) of the standard antioxidant BHT at the same concentration (Ramesh et al., 2009). The aqueous extract of *S. alternifolium* also efficiently scavenged the ABTS+ free radicals equally with the BHT. The scavenging activity was increased in a concentration-dependent manner of the extract as well as BHT. Maximum (96%) activity for the extract and (95%) for BHT was found at the concentration of 250 µg/ml (Ramesh et al., 2009). Another class of free radicals, nitric oxide (NO), was also significantly scavenged by the aqueous extract of *S. alternifolium* seeds at various concentrations (25, 50, 75, 100, and 250 µg/ml). The highest (47%) activity was observed at the concentration of 100 µg/ml, whereas BHT inhibited only 14% at the same concentration (Ramesh et al., 2009).

Hexane (HE), ethyl acetate (EAE), ethanol (EE), and water extracts (WE) of *S. alternifolium* (SA) leaf had shown potent antioxidant activity. All these extracts and gallic acid had shown DPPH-reducing activity in a dose-dependent manner. The highest DPPH scavenging activity was shown by water extract (IC_{50} 4 µg/ml) and second highest was found with ethanol extract (IC_{50} 60 µg/ml). The water extract of SA also had potent hydrogen peroxide radical scavenging activity. In the same way, SA leaf extracts also possess significant NO scavenging activity in a concentration-dependent manner (Ratnam et al., 2015). This antioxidant activity was due to the presence of high (29 ± 0.4%) quantity of total phenolic compounds in ethanol and aqueous (30 ± 0.8%) extracts.

71.3.2 ANTI-DIABETIC ACTIVITY

Treatment of Alloxan-induced diabetic rats with aqueous extract of *S. alternifolium* seeds at the dose of 0.75 g/kg.b.w had shown maximum blood glucose lowering effect (Kameswara Rao and Appa Rao, 2001). Administration of fraction C (50 mg/kg.b.w) of aqueous extract of SA seeds to the STZ-induced diabetic albino Wistar rats for 30 days effectively reduced their blood glucose levels, HbA1c and increased the plasma insulin levels, hemoglobin levels, bodyweights, and hepatic glycogen. At the same time, total cholesterol (TC), triglycerides, LDL-cholesterol, and VLDL-cholesterol levels were significantly decreased, whereas HDL-cholesterol levels were increased in treated diabetic rats (Kasetti et al., 2010).

Long-term treatment of diabetic rats with fraction C also showed its effect on carbohydrate metabolizing enzymes. The activities of hexokinase (HK) and Glucose 6-phosphate dehydrogenase (G6PDH) were significantly increased while the activities of gluconeogenic enzymes glucose 6 phosphatase (G6pase) and fructose 1, 6 bis phosphatase (F16Bpase) were significantly decreased in the liver and kidney of the experimental animals (Kasetti et al., 2012).

In diabetic rats, the activities of hepatic function markers SGOT, SGPT, ALP, and renal function markers serum urea and creatinine were notably increased compared to the normal rats. After the treatment with fraction C, the activities of the hepatic enzymes and serum urea and creatinine were decreased near to normal levels compared to the untreated diabetic rats. All the above antihyperglycemic or antidiabetic activities of fraction C of Aqueous extract of *Syzygium alternifolium* were because of a phenolic compound cinnamic acid and other-active principles present in the fraction C. It could exhibit its activity because of its stimulatory effect on remnant β-cells, resulting in increased insulin secretion, and increasing the peripheral utilization of glucose, or by decreasing the hepatic glucose production by inhibiting the gluconeogenesis (Kasetti et al., 2012). The antidiabetic properties of *S. alternifolium* are shown in Figure 71.1.

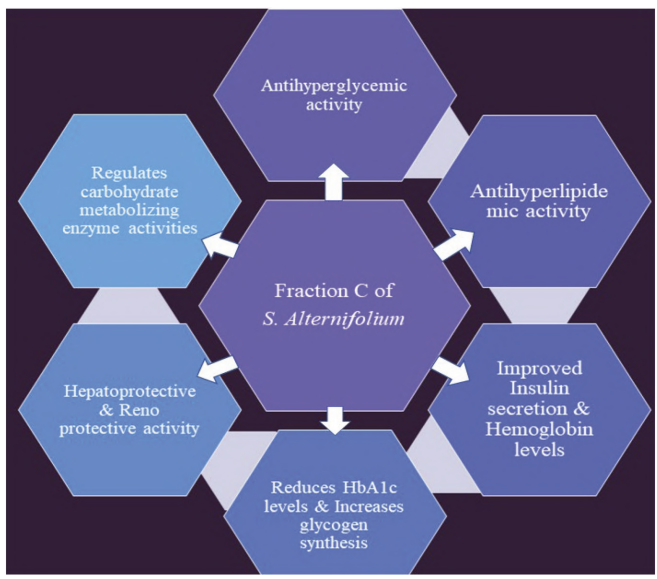


FIGURE 71.1 Antidiabetic properties of *S. alternifolium.*

71.3.3 ANTI-MICROBIAL ACTIVITY OF S. ALTERNIFOLIUM

S. alternifolium leaf extracts also exhibited strong antimicrobial activity. Hexane extracts (HE), EAE, and ethanol extracts strongly inhibit the gram-negative bacteria *Klebsiella pneumoniae* (Ratnam et al., 2015). This potential activity of SA was due to the presence of flavonoids (eucalyptin and tefrowastin) and terpenoids (Pulla Reddy et al., 2005). Eucalyptin was previously reported for its antimicrobial activity (Takahashi et al., 2004).

Similarly, petroleum ether extract of SA leaf exerts maximum antimicrobial activity against all the pathogens, except *S. aureus* and *C. albicans*. It was found that gram-negative bacteria, *E. coli* and *K. pneumoniae* were more susceptible than the gram-positive bacteria *Bacillus cereus* and *S. aureus* (Kumar and Yasmeen, 2013; Raju and Ratnam, 2008). ME of SA stem at the concentration of 60 mg/ml has shown highest antibacterial activity against *Pseudomonas auriginosa* (15.2 mm) and *Bacillus subtilis* (13.5 mm) (Ramireddy et al., 2017).

71.3.4 ANTIMICROBIAL POTENTIAL OF SILVER NANOPARTICLES SYNTHESIZED FROM THE STEM BARK OF S. ALTERNIFOLIUM

The silver nanoparticles synthesized from aqueous extract of stem bark of *S. alternifolium* had shown significant antibacterial activity against two-gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* and five-gram negative bacterial strains like *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhimurium*, and *Proteus vulgaris*. The order of the highest zone of inhibition activity of SNPs on bacterial strains growing on nutrient agar medium was as follows. *S. typhimurium* > *P. vulgaris*> *K. pneumoniae*> *E. coli*> *P. aeruginosa*> *B. subtilis*> *S. aureus*. Because of the spherical shape, nanosizes ranging from 4 to 48 nm and without agglomeration, the polydisperse green-synthesized SNPs exhibit a broad spectrum of antimicrobial activity against the bacterial and fungal strains (Yugandhar et al., 2015).

71.3.5 ANTIMICROBIAL ACTIVITY OF GREEN SYNTHESIZED COPPER OXIDE NANOPARTICLES OF S. ALTERNIFOLIUM

The green synthesized CuO NPs from the aqueous extract of stem bark of *S. alternifolium* plant powder had excellent antimicrobial activity. These

CuO NPs have shown the highest zone of inhibition towards *E. coli*, a gram-negative bacterium, and *S. aureus*, a gram-positive bacterium. This antimicrobial activity of CuO NPs was attributed to the phenols and proteins that are present in the stem bark aqueous extract (Yugandhar and Savithramma, 2017).

71.3.6 ANTI-CANCER ACTIVITY OF CUO NPS OF S. ALTERNIFOLIUM

From the results got, it was found that 5–13 nm size, spherical-shaped CuO NPs from aqueous extract of *S. alternifolium* stem bark had significant cytotoxic activity against the MDA-MB-231 human breast cancer cell lines. The 50% (IC_{50}) inhibition of treated MDA-MB-231 cell lines was observed at the concentration of 50 µg/ml when compared with doxorubicin, a chemotherapy medication used to treat cancer (Yugandhar and Savithramma, 2017).

71.3.7 ANTI-ULCER ACTIVITY OF S. ALTERNIFOLIUM

The ethanol extract of fruits of *S. alternifolium* possesses significant (68.04%) anti-ulcer activity at the dose of 500 mg/kg.b.w in albino rats with ethanol-induced ulcers. This protective effect of *S. alternifolium* was less than that of omeprazole which has shown an 80.60% protective effect at the dose of 20 mg/kg.b.w. The mechanisms responsible for the anti-ulcer activity could be the increased gastric mucosal defense through an increase in mucus or by increased bicarbonate production or maybe because of the decrease in the volume of gastric acid secretion or by neutralizing the gastric acid by the effect of ethanol extract of *S. alternifolium* (Priyadarsini et al., 2016).

71.3.8 IN VITRO AND IN VIVO ANTI-INFLAMMATORY ACTIVITY OF S. ALTERNIFOLIUM

The chloroform and MEs of *S. alternifolium* roots were reported to possess the anti-inflammatory activity in Wistar rats and mice (Kandati et al., 2012). It was found that in *in-vitro* 5-lipooxygenase (LOX) inhibition assay the chloroform extract (CE) exhibited the IC_{50} value 8.83 µg/m which was nearer to that of the standard drug zileutin (4.36 µg/ml), confirming that CE of *S. alternifolium* was suitable for *in vivo* anti-inflammatory studies. While

in vivo studies, chloroform and MEs of SA roots at the doses of 250 and 500 mg/kg significantly decreased the carrageenan-induced paw edema after 1.5, 2nd, 3rd, and 4th h of administration of the plant extract, and it was almost similar to the activity of the standard drug diclofenac sodium at 2nd, 3rd, and 4th h of administration. Among the two solvent extracts of *S. alternifolium* roots, CE has shown the highest anti-inflammatory activity in comparison to ME. The CE of *S. alternifolium* has also effectively decreased (swelling thickness: 120.25 ± 16.2 μM) the 12-o tetradeacanoylphorbol-13-acetate (TPA) induced mouse ear edema in comparison to the ME (swelling thickness: 155.80 ± 13.2 μM). Another *in vivo* study with acetic acid-induced writhes in albino mice with different doses of chloroform and MEs has shown that CE at the dose of 1,000 mg/kg significantly reduced the number of writhes than the ME, proving its potent anti-inflammatory activity. But it was less than the standard drug diclofenac (40 mg/kg).

KEYWORDS

- **anti-inflammatory activity**
- **antidiabetic activity**
- **hexane extracts**
- **lipoxygenase**
- **reactive oxygen species**
- ***Syzygium alternifolium***

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CHAPTER 72

Bioactives and Phytopharmacological Significance of *Triumfetta rhomboidea* Jacq.

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72.1 INTRODUCTION

Triumfetta rhomboidea Jacq. (Family: Malvaceae) is distributed throughout tropical and subtropical India, up to 1,200 m in the Himalayas. It is extremely far-reaching in mainland Africa, including South Africa. It is presented and adopted in Cape Verde, Madagascar, Seychelles, Réunion, Mauritius, and in Australia. The plants are small to medium-sized aromatic shrubs of 75–150 cm in height. It is commonly called burweed, Chinese bur, diamond burbark, but has different vernacular names in the regions of its distribution and also in diverse portions of the biosphere (Mevy et al., 2006; Khare, 2007). Leaves are orbicular, lower leaves 3-lobed, upper entire, ovate, acute, serrate, and clothed with stellate hairs on both surfaces. The yellow flowers are in dense, terminal, and leaf-opposed cymes. Fruit is a globose capsule, pubescent, and spinescent. The plant grows in a wide range of habitats in the open and cultivated fields, roadsides, wastelands, woodland margins, open forest and hilly places. The various parts of the plant extracts, including the flower, leaves, bark, root, fruit, and seeds of *T. rhomboidea*, are commonly used in many therapeutic drugs (Kubmarawa and Enwerem, 2006). They are respectable to rise the hunger, as intestinal assistance, liver stimulant, as gastrointestinal prokinetic agent, and mild laxative.

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Powders extracted from this plant are useful drugs and are used as an anti-ischemic and cardioprotective agent in hypertension, ischemic heart diseases and myocardial infection. These are useful in alleviating the pain of angina pectoris and treating heart failure diseases. They also are helping in curing renal calculi, retention of urine, leprosy, vomiting, enlarged spleen and liver, carious teeth, bleeding gums and spitting of blood from the chest. They are extremely useful in battling skin issues with releases like sensitivities and other erythematous issues (Mevy et al., 2006; Khare, 2007). Many secondary metabolites are cytotoxic in nature and are used as chemical warfare to fight against many diseases (Hunter, 2008). The natural products many times are used in pharmacological or natural action that can be utilized in therapeutic drug to treat many diseases because they contain active compounds (Samuelson, 2010). The people from Kenya and Tanzania employed the plant root for infusing the affected site of the snake bite (Bethwell and Daniel, 2006). The underground parts of this plant have been customarily utilized in the handling of dysentery as a diuretic in many parts of the world (Boily and Van Puyvelde, 1986). The roots of this species are used to treat intestinal ulcers, and observed that this is more effective compared with other treatments. The flowers and fruits of *T. rhomboidea* have been used in gonorrhea and leprosy treatment, whereas in East Africa, crushed leaves of the plant are used in the treatment of anemia (Okujagu, 2006).

72.2 BIOACTIVES

T. rhomboidea extracts form the traditional usage of these medicinal plants in the Western Ghats of India. The plant is having major organic chemical like α-humulene (8.5%), β-caryophyllene (28.9%) and oxygenated monoterpenes (69.5%) along with some minor compounds. This shows that the plant is having very good potential volatile organic compounds (Joshi, 2020).

The fundamental oil of the upper portions of *T. rhomboidea* was examined by GC and GC-MS and tested for its antimicrobial actions. The chief compositions detected were trans-β-caryophyllene (22.4%), kessane (14%) and caryophyllene oxide (13%) (Mevy et al., 2006). The construction of triumboidin was extracted from *T. rhomboidea* as scutellarein 7-O-l.-arabinorhamnoside. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and fast atom bombardment mass spectrometry (FAB-MS) information confirmed the structure of scutellarein 7-0-a-L-rhamnoside (Nair et al., 1986).

A new compound triumfettamide B, along with lupeol, β-sitosterol, stigmasterol, oleanolic acid, maslinic acid, β-sitosterol glucopyranoside, and trans-tiliroside have been isolated and identified from *T. rhomboidea* (Tchoukoua et al., 2013). The aerial parts of *T. rhomboidea* have been reported trans-β-caryophyllene, kessane, and caryophyllene oxide as the major constituents. Several researchers reported phytochemical analysis of *T. rhomboidea* species across the globe. The consequence of the initial phytochemical broadcast exposed the existence of saponins, flavonoids, carbohydrates, tannins, alkaloids, and terpenoids. Phytochemical broadcasting discovered the existence of flavonoids, steroids, triterpenoids alkaloids, tannins, and saponins in *T. rhomboidea* leaf cutting (Uche and Okunna, 2009; Hemalatha et al., 2015).

Phytochemical ingredients of 35 selected antitumor therapeutic plant isolates were evaluated by thin layer chromatography (TLC) for alkaloids, anthraquinones, xanthines, valepotriates, cardiac glycosides, flavonoids, essential oils (EOs), coumarins, lignans, saponins, and arbutin compounds. These plants obtained from Kakamega tropical rain forest have been recently answered to be utilized for disease treatment in the Kakamega County, Kenya. The phytochemical spreading in the 35 plants encompassed 71.4% alkaloids, 57.1% anthraquinones, 94.2% xanthines, 82.8% valepotriates, 94.2% cardioactive glycosides, 82.8% flavonoids, 77.1% EOs, 85.7% coumarin drugs, 68.5% lignans, 80% saponins and 62.85% arbutin drugs. Thus, the raw organic and inorganic solvent isolates of these examined plants comprise therapeutically significant bioactive mixtures (Ochwang'I et al., 2016).

72.3 PHARMACOLOGY

The plant possesses cytotoxic effects, antioxidant, and antimicrobial activities (Hemalatha et al., 2015), analgesic activity and anti-inflammatory effect (Geissler et al., 2002; Pradhan et al., 2003; Bessiere et al., 2006; Devmurari et al., 2010).

72.3.1 ANTIMICROBIAL ACTIVITY

EOs isolated from *T. rhomboidea* revealed to hold antimicrobial action. The MEs have also been shown to have antioxidant and antitumor activity *in vivo*. The methanolic extract of *T. rhomboidea* leaves shows antimicrobial activity against *Staphylococcus aureus, Salmonella typhi* and *Klebsiella*

pneumoniae. The rough concentrate shows a generous antimicrobial action against *K. pneumoniae* (documented as the best affectability), *S. typhi* and not against *S. aureus*. The consequence of the intuitive investigations between the unrefined concentrate and standard anti-infection agents showed relationship going from threat to collaboration. Phytochemical investigation uncovered the existence of terpenes, flavonoids, and other phenolics and resins in the raw isolate. Along these lines, *T. rhomboidea* holds auspicious disinfectant action particularly against *K. pneumoniae* (Odimegwu et al., 2011).

72.3.2 LACTOGENIC ACTIVITY

Sahoo et al. (2016) assessed the lactogenic action of fluid concentrate of *T. rhomboidea* (ATRR) on nursing rodents. Oral insertion of ATRR expands the milk yield, body weight of little guys just as mother rodent, glycogen, and protein content just as serum prolactin and cortisol level when contrasted with the control creatures. The lactogenic consequence of ATRR followed portion subordinate way when contrasted with control. Subsequently, ATRR has huge lactogenic action by improving milk creation and prolactin fixation in nursing rodents.

72.3.3 ANTITUMOR ACTIVITY

Sivakumar et al. (2010) studied the antitumor and antioxidant activities of ME of *T. rhomboidea* (METR) leaves against Ehrlich ascites carcinoma (EAC) attitude Swiss. The METR managed at the dosages of 100, 200 mg/kg, in mice for 14 days following 24 hours of growth immunization. The impacts of METR on the development of murine cancer, life length of EAC bearing mice were examined. Hematological profile and liver biochemical boundaries (lipid peroxidation (LPO), cancer prevention agent chemicals) were likewise assessed. Treatment with METR diminished the cancer volume and practical cell count thereby expanding the life expectancy of EAC bearing mice. METR brought back the hematological boundary pretty much typical level. The impact of METR additionally diminishes the degrees of LPO and expanded the degrees of glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT).

Estella et al. (2017) assessed the cytotoxic impacts of this therapeutic plant utilizing both MTT and unbiased red tests. Hep G2 cells were presented

to extracts taken from plant species at concentration of 0.1, 1, 10, and 100 µg/ml and the cytotoxic not really settled utilizing both MTT and Neutral Red tests. MTT test for cells treated with different convergences of the methanol unrefined concentrate of the leaf of *T. rhomboidea* showed a huge contrast between control tests and those treated with 1 µg/ml, 10 µg/ml and 100 µg/ml of test. Also, huge contrasts were seen between tests treated with 0.1 µg/ml and 10 µg/ml and 100 µg/ml of test. The unbiased red test for this species showed no huge distinction in absorbance levels between control tests, and those treated with any grouping of the plant remove tried. In any case, huge contrasts were identified for this species in the unbiased red examine between tests treated with 0.1 µg/ml of concentrate and 10 µg/ml extricate, notwithstanding critical contrasts being recognized in examples treated with 0.1 µg/ml and 100 µg/ml of concentrate.

The cytotoxic action of unrefined concentrate, portions, and a few mixtures of *T. rhomboidea* stems were considered in contrast to human fibrosarcoma disease cell line HT1080 utilizing stream cytometry. The ethyl acetic acid derivation division showed feeble action while the unrefined concentrate and the hexane and n-butanol parts introduced under half of cell development restraint (Tchoukoua et al., 2013).

72.3.4 ANTIDIABETIC ACTIVITY

Duganath et al. (2011) studied the antidiabetic impact of ethanolic extract of *T. rhomboidea* in alloxan-incited diabetes rodents. Oral organization of ethanolic extract of *T. rhomboidea* at the portions of 100, 200, and 400 mg/kg body weight was tested in alloxan actuated diabetic rodents. The antidiabetic impact of plant extract was expanding with expansion in portion. At 400 mg/kg body weight ethanolic extract showed huge abatement in the blood glucose levels. Thus, the ethanolic extract (EE) of *T. rhomboidea* possess significant antidiabetic activity.

72.3.5 ANTI-INFLAMMATORY ACTIVITY

Thawkar et al. (2016) showed the *in-vitro* effect by membrane stabilizing on human red blood cells and protein denaturation activity using 70% ethanol extract. The anti-inflammatory activity of *T. rhomboidea* plant shows 208% of inhibitory effect on protein denaturation as compared with control. The plant extract also produces 34.7% inhibition of RBC hemolysis as compared

with 68.66% produced by diclofenac sodium when induced on hypotonic solution in erythrocyte membrane. The extract of this plant shows good effect in prevention on anti-inflammatory, increase the platelet and also support the cell.

72.3.6 ANALGESIC ACTIVITY

Uche and Okunna (2009) inspected the pain relieving and calming impacts of the methanolic concentrate of the leaves of *T. rhomboidea* on mice and rodents individually. *Triumfetta rhomboidea* leaf extract (50,400 mg/kg) caused a measurably critical hindrance on the egg whites incited edema or irritation in Wister pale skinned person rodents. Moreover, *T. rhomboidea* extract caused a measurably critical decrease in the quantity of acidic corrosive instigated squirming in mice. These impacts were additionally portion reliant and more prominent than the pain-relieving impacts by paracetamol which was utilized as a kind of perspective medication. Subsequently, *T. rhomboidea* can be suggested for intense fiery issues and sicknesses related with torments.

72.3.7 ANTIOXIDANT ACTIVITY

Triumfetta rhomboidea pull remove needed for IC_{50} was 336.65 ug/ml, 1346.03 ug/ml and 1004.22 ug/ml for superoxide rummaging, hydroxyl revolutionary searching and LPO individually. In this way, *T. rhomboidea* had huge cell reinforcement movement (Lissy et al., 2006).

72.3.8 ANTI-STERILE ACTIVITY

The effects of aqueous extracts of *T. rhomboidea* (TR) leaves on hormonal and male ripeness work was researched in male guinea pigs by Momo et al. (2020). Semen examination was done for the assurance of the centralization of spermatozoa, sperm motility, rates of unusual sperm cells (sperm morphology) and trash. In this manner, the watery concentrate of TR altogether expanded the basal degree of serum testosterone with practically no impact on the serum levels of luteinizing chemical (LH), follicle animating chemical (FSH), and prolactin of the male guinea pig. The organization of 400 mg/kg of TR extract increased the sperm count from 61.25±1.25 (control

creatures) to 81.75±2.02 (14 days) and 98.75±4.2 (28 days). Be that as it may, 25–400 mg/kg of the concentrate controlled over the diverse length of the review had no impact on the sperm motility, sperm morphology and sperm flotsam and jetsam separately. *Triumfetta rhomboidea* over various occasions of openings (7–28 days) prompted gentle, moderate to seriously diffused and summed up macrovesicular steatosis in a period – subordinate modifications of the different organs' histology contrasted with the controls. Henceforth, the watery concentrate of TR might be helpful in treating richness issues related with oligospermia (low sperm count) and low testosterone levels.

KEYWORDS

- **antitumor activity**
- **bioactives**
- **methanol extract**
- **nuclear magnetic resonance**
- **superoxide dismutase**
- **thin layer chromatography**
- ***Triumfetta rhomboidea***

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CHAPTER 73

Bioactive Components and Pharmacology of *Wrightia arborea* (Dennst.) Mabb.

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73.1 INTRODUCTION

Wrightia arborea (Dennst.) Mabb. (Syn. *Wrightia tomentosa* Roem. & Schult.) is commonly called Wooly Dyeing Rosebay, jaundice curative tree, bitter indrajao and dyer's oleander, belongs to the family Apocynaceae. It is found in warm parts of India, Myanmar, Sri Lanka, and Thailand. It's a deciduous tree that grows around 20 meters high with small branches and their leaves are oppositely arranged, elliptic or obovate. The trunk may have a diameter of 35 cm. The bark is thick and gray. The flowers are pale yellow or yellowish brown in color which matures into dull purple color, and they have an unpleasant smell. In Africa, it is occasionally cultivated as an ornamental.

In the traditional medicine, *Wrightia arborea* has been used for curing cancer (Bhattacharya, 2006), antipyretic, and hemostatic (Jamir and Takatemjen, 2010), amebic dysentery, menstrual irregularities, renal abnormalities (Rastogi and Dhawan, 2004; Jayaswal and Basu, 1965). Bark, roots, and stems from this plant in India is used for treating snake bite (Nyman et al., 1998; Mishra et al., 2016) and scorpion venom envenoming (Hutt and Houghton, 1998). Leaf extracts for hypertension treatment (Rajendran et al., 2003). Devi et al. (2017) reported that this plant cures diseases of skin, thirst, pittam, and vatam, dysentery, piles, psoriasis, eczema, worm infestation, venereal diseases, leprosy, and diarrhea.

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73.2 BIOACTIVE COMPOUNDS

73.2.1 PHYTOCHEMICAL SCREENING

Phytochemical screening was carried out in leaves, stem, bark, root, and fruit of *Wrightia arborea* (WA) plant using different solvents which are described as follows. Zaki et al. (1981) studied the phytochemicals in WA plants and found triterpenes, unsaturated sterols, phenolic acids, flavonoids, and alkaloids. Kokate (1994) analyzed the phytochemicals qualitatively in ethanolic leaf and bark extracts of WA and found mucilages, alkaloids, flavonoids, gums, and fats and oils. Nagarajan et al. (2006) analyzed preliminary phytochemicals in the butanol and ethanol extracts of WA bark and leaf. They found the presence of alkaloids, fats, and oils in bark and presence of terpenoids and flavonoids in the leaf extracts of butanol, respectively. Alkaloids, fats, oils, gums, and mucilages are present in higher quantities in the ethanolic extract (EE) of leaves whereas the plant's ethanolic bark extract was high in gums and mucilages, as well as fats and oils, and had a moderate amount of alkaloids.

Nagarajan et al. (2008a) studied phytochemicals in ethanolic leaf and bark extracts of WA which showed the presence of alkaloids in leaf EE and flavonoids in ethanolic bark extract as predominant active constituents, respectively. The content of total phenolics and flavonoids are present in large amounts in the ethanolic bark extract when compared to the leaf extract. WA leaf, stem, and fruit ethyl acetate (EAE), petroleum ether, methanol, and water extracts (WEs) were tested for phytochemicals, content of total phenol, and flavonoids (Kaneria et al., 2009). Highest flavonoid content was shown by EAE extract and petroleum ether extract of stem, respectively. Cardiovascular glycosides and triterpenes were detected in higher concentrations than other phytoconstituents.

Phytochemical screening of n-hexane extract from WA root showed the presence of flavonoids for WTRHF7 and protein for WTRHF4 as major active constituents along with saponins, alkaloids, glycosides, and steroids (Nagarajan et al., 2012). Further, they have identified WTRHF7 as mangiferin and WTRHF4 as amyloid β-protein (Aβ17-28) by physical, chemical, and spectral characteristics. Srinivas et al. (2013) screened phytochemicals in different solvent extracts, i.e., methanolic, chloroform, petroleum ether, EAE and aqueous extracts of WT leaf. According to the findings, methanolic leaf extract contained ellagic acids, alkaloids, methylene dioxy compounds, iridoids, steroids, triterpenoids, and tannins.

Sharma et al. in 2017, studied, and compared the phytochemicals in four different species of *Wrightia.* The findings revealed glycoside, quinines, anthocyanins, cardiac aurones, flavonoids, calcones, and catchins in the methanolic extracts of leaves of *W. coccinea, W. tinctoria, W. mollissima* and *W. arborea* and absence of saponin, tannin, anthraquinone, and alkaloids in all the four species. However, lucoanthocyanin, and indole were also present in *W. arborea.*

Ahirwar et al. (2019) studied the phytochemicals in aqueous, methanol, and chloroform extracts (CEs) of WA leaves. The results showed the presence of resins, carbohydrates, glycoside, flavonoids while starch and proteins are absent in all extracts. Ahirwar et al. (2020) compared the phytochemicals present in leaf, stem bark and root bark of *Wrightia arborea*, *Wrightia tinctoria* R. Br. and *Holarrhena antidysenterica* (Roth) Wall ex. A. DC., by gravimetric and spectrophotometric methods. They found highest content of alkaloids, flavonoid, saponin, and crude protein in HALT, WTLH, HARBT, WTRBH by gravimetric method and highest content of total carbohydrate, soluble protein, tannin, and alkaloid in HASBT, HALT, HARBC, and WTLH by spectrophotometric method.

Phytochemical studies of Daniel and Sabnis (1978, 1982), Lin et al. (1992), and Khyade (2006) stated that there are glycoflavones-iso-orientin, flavonoids, terpenoids, steroids, tannins, saponins, phenolic acids, wrightiadione, alkaloids, and isoflavone in leaves of *W. arborea*. Khare (2007) and Khyade and Vaikos (2011) found conessine dihydrate, kurchicine holarrhine and conkurchine alkaloids, α-amyrin, flavonoids, lupeol, tannins, phlobatannins, simple phenolics, β-sitosterol and reducing sugars in a very minute quantity in *W. arborea* bark.

Khyade and Vaikos (2011) found tannins, phenolics, flavonoids, saponins, alkaloids, and cardiac glycosides, triterpenoids (Kaneria et al., 2009) in bark extracts of *W. arborea.* Lakshmi Devi and Sri Ramakrishna (2012) studies on phytochemicals indicated triterpenoids, tannins, flavonoides, steroids, and alkaloids in the EE of *W. arborea*.

Khyade and Vaikos's (2014) preliminary screening of phytochemicals indicated flavonoids, phlobatannin, alkaloids in leaves and bark; tannins, reducing sugars, saponins, phenolics in root, bark, and leaves; terpenoid, steroids, leucoanthocyanins, and iridoids in only leaves. Higher amounts of tannins, saponin, calcium, and minerals were detected in leaves than others. Anuj Kumar et al. (2017) made qualitative phytochemical analysis and confirmed the presence of alkaloids, flavonoids, terpenoid, leukoanthocyanins, indole, quinone, oxalic acid, anthocyanins, aurones, calcones,

catchins, and cardiac glycoside in *W. arborea.* Lakshmipriya et al. (2017) detected the total phenolic and flavonoid content in *W. arborea* leaf extract. Compared with other extracts, methanolic extracts showed higher phenolic and flavonoid content.

73.2.2 BIOACTIVE COMPOUNDS

Maiti and Beri (1962) isolated and identified alpha-Amyrin, a triterpenoid from bark extracts of WA. Jayaswal and Basu (1965) identified alkaloids in the WT bark using chloroform: n amyl alcohol: alcohol: water (9:8:5:2). Muruganandam et al. (2000) investigated chemical constituents in genus *Wrightia,* viz., *W. tinctoira, W. coccinea*, and *W. arborea* to locate their bioactive principles in fresh and preserved leaves at different periods of vegetation. They have isolated and identified indirubin 6, indigotin 3, isatin 5, tryptanthrin 8, anthranillate 7 and rutin 9 as major phytoconstituents in *W. tinctoria* and *W. arborea*.

Tryptanthrin is found to be a native compound in *Wrightia*. Honda et al. (1979) concluded that it is the stress metabolite of the producer plant and is a strong antimicrobial agent that fends off predators from *Wrightia* sps., when they are highly vulnerable to extraneous stresses. Bhattacharya et al. (1991) detected isatin, a component of tribulin, an endogenous marker of stress and a proven MAO inhibitor for the first time in fresh and dried leaves of *W. tinctoria* and WA.

The known biological profiles of indole metabolites (Tang and Eisenbrand, 1992; Honda et al., 1979; Bhattacharya et al., 1991) and findings of Muruganandam et al. (2000) suggest that the antimicrobial activity of *Wrightia* may be attributed to tryptanthrin (Honda et al., 1979), antileukemic activity to indirubin (Tang and Eisenbrand, 1992), and antioxidant activity to rutin (Chen, 1990), indigotin, and indirubin. Muruganandam et al. (2000) concluded that the antioxidative, antiproliferative, and antimicrobial principles of *Wrightia* would seem to account for its therapeutic effect in the treatment of psoriasis. Kunz and Kress (1927) suggested that the rich supply of oxygen ensured by indigotin would seem to account for the beneficial effects of *Wrightia* extracts as immuno-modulatory agents. Nagarajan et al. (2012) identified and characterized the amyloid β-protein (Aβ17-28) and mangiferin from the n-hexane root extracts of WT. Maurya et al. (2012) identified compounds that are anti-dyslipidemic such as β-amyrin palmitate and β-amyrin acetate and in EE and fractions of WA leaves and demonstrated

the new property to them as an agent that lowers the lipid content. Nagalakshmi and Murthy (2015) reported squalene, γ tocopherol, campesterol, lupeol, phytol in seed oil of *W. arborea*.

73.3 PHARMACOLOGY

73.3.1 ANTIMICROBIAL ACTIVITY

Jain et al. (1987) isolated fatty oil from WA seeds and showed its potent antibacterial efficiency against various strains of bacteria such as *S. paratyphi, B. subtilis* and *S. typhi.* Nagarajan et al. (2006) used the technique of disc diffusion in order to test the antimicrobial efficacy of butanol and ethanol extracts of WA leaves and stem bark, as well as its isolates of seven pure components (BLF28, ELF7, BBF29, EBF7, BLF29, ELF17, ELF3), post-column chromatography fractionation, against *S. faecalis, S. albus, S. aureus*, and *B. subtilis;* and *Proteus vulgaris, Klebsiella aerogenes, Pseudomonas aeruginosa,* and *E. coli*, as well as the fungus *Candida albicans*. The activity of the extracts and isolates against pathogenic microbes varied. The butanol extracts of bark (BBF29) and leaves (BLF 29) are much more efficient than the extracts of ethanol and bark and leaf in suppressing all the microbial strains.

Mahida and Mohan (2007) have screened the antibacterial activity of WA against *Salmonella* and *Staphylococcus* species and found ME of this plant demonstrated remarkable antibacterial activity against *S. paratyphii* A and *S. aureus*. Kaneria et al. (2009) evaluated the antibacterial activity of leaves, stem, and fruit of WA with various extracts of solvents like EAE, methanol, water, and petroleum ether against *Pseudomonas aeruginosa, Bacillus subtilis, Enterobacter aerogenes, Staphylococcus aureus* and *Salmonella typhimurium.* Best antibacterial activity in leaf and fruit and the highest antibacterial activity of leaf EAE extract against *S. aureus* was observed from the results.

Nagarajan (2010) evaluated the antimicrobial activity of WA stem ethanol extract against *Candida albicans* (fungi), *S. faecalis, S. aureus* and *B. subtilis* and *E. coli* and *P. aeruginosa* by disc diffusion technique. Results showed partial resistance against *E. coli* (1 mm) and *S. faecalis* (2 mm) whereas complete resistance against *P. aeruginosa, S. aureus*, *B. subtilis* and *C. albicans.* They came to the conclusion that WA stem extract's antimicrobial activity was mostly due to mutations in bacterial DNA gyrase's unique

binding sites, which reduced stem extract's effectiveness. They proposed that the WA stem extract be used with other herbal drug species as a combination remedy to prevent drug resistance in the near future.

Srinivas et al. (2013) studied the antibacterial properties of various solvent extracts of WA leaf., like EAE, aqueous, chloroform, methanolic, and petroleum ether using the well diffusion technique against bacteria. Chloroform, EAE and methanolic extracts have the greatest susceptibility of all the leaf extracts tested. There was no antimicrobial activity in the aqueous extract. Ahirwar et al. (2019) assessed the antibacterial activity of methanol, aqueous, and chloroform leaf extracts of WA and discovered that the methanolic extracts of WA leaves have higher antibacterial activity.

Divakara and Lakshmi Devi (2010) tested individual extracts of aqueous, EAE, dichloromethane (DCM), methanol, petroleum ether, 70% ethanol and chloroform of *W. arborea* leaf by using the cup plate method to test their antibacterial activity *in vitro* against *Staphylococcus aureus, Staphylococcus epidermidis*, *Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa*. More antibacterial activity was found in ME compared to other extracts.

Khyade and Vaikos (2011) tested acetone, petroleum ether, chloroform, and MEs of *W. arborea* bark against *Micrococcus luteus, Escherichia coli, Klebsiella planticola, Bacillus megaterium, Bacillus subtilis, Salmonella typhi, Staphylococcus aureus* and *Pseudomonas aeruginosa*. Broader spectrum of antimicrobial activity was exhibited by chloroform, acetone, and methanol except petroleum ether extracts. All the extracts exhibited significant antibacterial activities against all the tested bacteria and CE showed activity particularly, to *M. luteus, S. aureus*, *S. typhi*, and *P. aeruginosa*. Lakshmipriya et al. (2017) found genus specific antimicrobial effects of all the extracts of *W. arborea* especially methanolic extract only against *Klebsiella* sp.

73.3.2 ANTIOXIDANT ACTIVITY

WA leaf, stem, and fruit DPPH free radical scavenging activity with various solvent extracts like EAE, petroleum ether, water, and methanol were determined by Kaneria et al. (2009). They found IC_{50} values of more than 1,000 µg/ml in EAE and petroleum ether extracts of stem, leaves, and all extracts of fruit. While the methanol and aqueous extracts of leaf revealed IC_{50} values of 530 and 205 µg/ml and 460 and 360 µg/ml for stem, respectively. Nagarajan

et al. (2008a) studied the antioxidant activity of leaves and bark alcoholic extract from WA. The results revealed WA bark possessed a good antioxidant property. The antioxidant potential of the ethanol bark extract (8.3 g vitamin E equivalent/mg) seems to be double that of the leaves extract (4.2 g vitamin E equivalent/mg).

More antioxidant activity with an EC_{50} value of 330 µg/ml in EAE extract of *W. arborea* leaf were reported by Lakshmipriya et al. (2017). However, they found antioxidant potential in chloroform, acetone, and methanol and petroleum ether extracts also.

73.3.3 CYTOTOXICITY

Lin et al. (1992) isolated wrightiadione from the WA plant, a novel isoflavone that showed cytotoxic effect against the P 388 lymphocytic leukemia cell line. This antileukemic activity is due to the presence of indirubin (Tang and Eisenbrand, 1992). Studies of Lakshmi Devi and Divakar (2010) concluded that Brine Shrimp Naupli are susceptible to methanolic and ethanolic leaf extracts of *W. arborea* (LC_{50} values – 531.082 and 498.213 µg/ml, respectively).

73.3.4 ANTIPROLIFERATIVE AND ANTICANCER ACTIVITY

Chakravarthy et al. (2012) tested the leaf EE, corresponding hexane fractions and fraction F-4 of WA for pro-apoptotic and antiproliferative activity in MDA-MB-231 and MCF-7. The results indicated cell inhibiting and pro-apoptotic activity in MDA-MB-231 and MCF-7 cells by WA leaf F-4 fraction and concluded it is because of ursolic acid and oleanolic acid presence along with wrightiadione isolated from WA, which had previously been shown to have anticancer properties by Lin et al. (1992). The extract's anticancer efficacy against breast cancer cells is also attributed for the initiation of the apoptotic pathway. Nagarajan et al. (2008d) compared the anti-tumor effects of ethanolic bark and leaf extract of WA in mice bearing Ehrlich ascites carcinoma (EAC) and found a potent antitumor effect in leaf extract of WA than the bark extract. On the other hand, *in vivo* antitumor activity of methanolic leaf extracts of *W. arborea* were reported by Zahan et al. (2013).

Lakshmipriya et al. (2017) assessed different leaf extracts of *W. arborea* like chloroform, acetone, EAE, methanol, and petroleum ether for antiproliferative properties. After 24 hours of exposure, antiproliferative activity was

exhibited by CE only against human leukemic K562 cells (with IC_{50} of 40 ± 3 μg/ml, that gradually reduced to 26 ± 2 μg/ml and 5 μg/ml after 48 and 72 hours of exposure, respectively). Lakshmipriya et al. (2018) evaluated the apoptotic/antiproliferative potential of *Wrightia arborea'*s acetone, chloroform, petroleum ether, methanol, and EAE leaf extracts on cancer cell lines. They found K562 cells were selectively killed by the chloroform extract (WAC) and no effect on Hep G2. MCF-7 cells, and normal human peripheral blood lymphocytes. Cytotoxicity was not exhibited by methanol, EAE and acetone extracts against Hep G2, K562 and MCF 7 cell lines.

73.3.5 ANTI-DYSLIPIDEMIC AND HMG-COA REDUCTASE INHIBITORY ACTIVITY

Maurya et al. (2012) tested leaves EE and fractions of WA for antidyslipidemic activity. They have identified compounds that are antidyslipidemic (β-amyrin palmitate, β-amyrin acetate) by activity guided isolation. At a dosage of 10 mg/kg, these compounds reduced LDL levels by 36% and 44%, respectively, and raised HDL-C/TC ratio by 49% and 28%, respectively. They also displayed strong inhibition of HMG-CoA-reductase, which was confirmed with docking tests. This study found that β-amyrin palmitate and β-amyrin acetate have a new property as a highly effective lipid-lowering agent.

73.3.6 ANTI-ALLODYNIC ACTIVITY

Nagarajan et al. (2007a) reported that the ethanolic leaf and bark extracts of WA showed anti-allodynic activity in Swiss Albino mice and no visible toxicity signs (Nagarajan et al., 2008a). The extracts of bark exhibited more anti-allodynic activity compared to leaf extracts which is due to the higher content of flavonoids present in bark compared to the leaves. Various flavonoids, including bioflavonoids, rutin, luteolin, quercetin, and hesperidin are demonstrated for anti-inflammatory and antinociceptive properties in other studies (Bittar, 2000; Galati et al., 1994; Calixto et al., 2000).

73.3.7 ANTITUBERCULAR ACTIVITY

Nagarajan et al. (2008b) evaluated the antitubercular activity of WA EEs of leaf and bark against *Mycobacterium tuberculosis* (MTB) H37Rv and *Mycobacterium* other than tuberculosis (MOTT) in a variety of dosages.

Rather than tuberculosis, they observed more positive findings against non-tuberculous mycobacterial infections (NTM), which are key challenges for hospitals and clinics. WA leaf extracts (100 mg) have been shown to have effective against MOTT, as growth observed (43.1 hours) is significantly higher than the control (11.9 hours). This is because of active constituents such as alkaloids and flavonoids. N-methyl pyrrole, a pure alkaloidal component isolated and identified from WT leaf, was evaluated *in vitro* against *Mycobacterium tuberculosis* using the Versa TREK rapid culture technique and found a time for positivity in 19.9 hours compared to control (Nagarajan et al., 2010).

73.3.8 ANTIPYRETIC ACTIVITY

David et al. (2010b) reported that the methanol: DCM (1:1) leaves extract of WA reduces pyrexia in albino rats induced by yeast.

73.3.9 ANTI-INFLAMMATORY ACTIVITY

David et al. (2010a) studied the anti-inflammatory activity of methanol: DCM (1:1) leaf extract of WA in dextran-induced edema in the paws of rats and observed the leaf extract substantially reduced the dextran-induced edema. Nahar et al. (2013) and Devi and Divakar (2012) reported that alcoholic extracts of *W. arborea* leaves have analgesic, anti-inflammatory, and wound-healing properties.

73.3.10 ANTINOCICEPTIVE ACTIVITY

Nagarajan et al. (2007b) tested ethanolic leaves and bark extract of WA for antinociceptive activity and acute toxicity in mice and found bark extract exhibited maximum antinociceptive activity and no activity with leaf extracts. Various flavonoids like luteolin, rutin, hesperidin, quercetin, and bioflavonoids are demonstrated to have anti-inflammatory and antinociceptive properties (Galati et al., 1994; Ramesh et al., 1998; Calixto et al., 2000; Bittar, 2000). Laizuman et al. (2013) reported *W. arborea* methanolic extract has anti-inflammatory and antinociceptive properties using various models in rats. They discovered powerful anti-inflammatory and analgesic properties that could be mediated by both central and peripheral mechanisms.

73.3.11 ANTIHYPERGLYCEMIC ACTIVITY

WA ethanolic bark extract showed strongest antihyperglycemic activity in streptozotocin (STZ)-induced diabetic rats (Nagarajan et al., 2008c).

73.3.12 ANTI-PSORIASIS ACTIVITY

Kharmawphlang and Sarma (2004) evaluated the efficacy of the indigenous drug (coconut oil extract of WA leaves) on psoriasis in Guwahati, Assam, and the results revealed relief to the patients by improving the disease's clinical signs.

73.3.13 WOUND HEALING ACTIVITY

Lakshmi Devi and Ramakrishna (2012) evaluated 70% EE of *W. arborea* leaves and the phytosome (WAP) prepared out from WAET using Wistar albino rats for the wound healing activity (WEAT). Remarkable wound healing capability was exhibited by the phytosome of WAT 4% than WEAT and standard 0.2% Nitrofurazone ointment.

73.4 CONCLUSIONS AND FUTURE PROSPECTS

Wrightia arborea (Dennst.) Mabb. (Syn. *Wrightia tomentosa* Roem. & Schult.) is commonly called Wooly Dyeing Rosebay, dyer's oleander, bitter indrajao and jaundice curative tree, belongs to Apocynaceae. It yields a yellow dye and wood is used in making toys and crafts. Many scientists have screened different parts of this plant for phytochemicals using different solvents. Bioactive compounds like alpha-amyrin, a triterpenoid from bark; indirubin 6, indigotin 3, isatin 5, tryptanthrin 8, anthranillate 7, and rutin 9 from leaves; amyloid β-protein (Aβ17-28) and mangiferin from n-hexane root extract and antidyslipidemic compounds such as β-amyrin palmitate and β-amyrin acetate from EE and fractions of leaves were isolated and identified. Also, therapeutic and pharmacological properties of these compounds are studied and enumerated. There is a scope to isolate and identify new bioactive compounds and determine their pharmacological properties, which may help in the cure of many human diseases that may pave the way to new drug discoveries.

KEYWORDS

- **Ehrlich ascites carcinoma**
- ***Mycobacterium tuberculosis***
- **non-tuberculous mycobacterial infections**
- **pharmacological properties**
- **tuberculosis**
- ***Wrightia arborea***

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CHAPTER 74

Bioactive Components and Pharmacology of *Wrightia pubescens* R.Br.

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74.1 INTRODUCTION

Wrightia pubescens R.Br. belongs to the Apocynaceae family. In Vietnam, it is commonly called long muc long and as "lanete" or "laniti" in the Philippines. It occurs in mainland China, Australia, Taiwan, Indonesia, New Guinea, the Philippines, Indochina, and India (Roskov et al., 2014). It is mainly seen in deciduous lowland thickets and forests. The main habitat of this plant is evergreen and deciduous forest and permanent dry location. It is a medium-sized to large evergreen tree that can reach a height of 35 meters. The columnar bole has a diameter of up to 50 cm and no buttresses.

This plant is included in preparation of Chinese medicines to treat various diseases like osteoarthritis (Ji and Liu, 2014; Jiang, 2012), acute upper respiratory infection which is seen in children (Song and Zhou, 2012) and intractable hiccups (Liu et al., 2014). In Malaka area, leaves, roots, and bark of this plant are used as an oral treatment to cure malaria (Taek et al., 2018). The roots and bark extract of this plant are utilized in traditional medicine to treat scrofula and rheumatic arthralgia (Van Sam et al., 2004) and the latex to cure dysentery (Song and Zhou, 2012). Apart from therapeutic uses, the bark of the plant is commonly used as a coagulant for manufacturing litsusu, a

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traditional cheese-like product in Indonesia; roots and bark in poultices; bark fibers in making paper and artificial cotton; wood (lanete) in carving, turnery, for general construction, pencils, musical instruments, wayang figures and carving (Lanete, 2017; Tropical Plants Database, 2021).

74.2 BIOACTIVE COMPOUNDS

Bioactive compounds like ursolic acid (Ragasa et al., 2014a), oleanolic acid (Rangasa et al., 2014), squalene (Tsai et al., 2012a), β-sitosterol (Rangasa et al., 2014) and chlorophyll α (Kim et al., 2014; Ragasa and de Jesus., 2014) were isolated and identified from the *W. pubsecens* leaves (Ragasa et al., 2014b) gathered from the DLSU-STU riparian forest. The oleanolic acid, α-amyrin acetate and ursolic acid (Ragasa et al., 2014b; Tsai et al., 2012b) and wrightiadone, an isoflavone (Ragasa et al., 2015) were reported in the twigs of this plant. On the other hand, Traxler et al. in 2021 analyzed stem bark of *Wrightia pubescens* and extracted two new compounds, tryptanthrin, an indole derived compound and a phenolic apio glucoside named kelampoyaside A.

The chemical constituents of *Wrightia pubescens* root were studied, and identified 12 compounds 1–12, i.e., coumarin, 4-hydroxybenzoic acid, ursonic acid, β-sitosterol, medioresinol, vanillic acid, mollugin, 4-hydroxymethyl-5-hydroxy-2H-pyran-2-one, vanillin, β-daucosterol, cleomiscosin B and scopolectin (Chen et al., 2017).

In 2017, Zuhrotun et al. screened phytochemicals in crude extract of *W. pubesens* and found kuinon, flavonoid, saponin, polyphenol, and triterpenoid while alkaloid, tannin, and steroid were absent. The medicinal values of bioactive compounds present in *Wrightia pubescens* are as in subsections.

74.2.1 URSOLIC ACID

Ursolic acid plays a significant role in growth and development. It activates caspases and regulates various other pathways, and it is also involved in cell proliferation and migration by inducing apoptosis (programmed cell death) in tumor cells (Wang et al., 2011); targets the STAT3 and impedes the growth of initiating cells for colon cancer (Wang et al., 2013); acts against HCT15 (human colon carcinoma cell line) by exhibiting antitumor activity (Li et al., 2002); inhibits proliferation and cell growth of Jurkat leukemic T-cells, and reduces the PMA/PHA induced TNF-α and IL-2 in a concentration and

time dependent manner (Kaewthawee et al., 2013); delays Cervical cancer cells' (TC-1) tumor development and activated autophagy induced cytotoxicity (Shen et al., 2014); is used as a potential therapeutic in prostate cancer because of its apoptotic and antiproliferative effects (Kassi et al., 2007).

74.2.2 OLEANOLIC ACID

Oleanolic acid inhibits hyperpermeability and the migration and adhesion of leukocytes, expression of CAMs and acts as an anti-inflammatory agent (Lee et al., 2013); it hinders the HMGB1 signaling pathway and shows anti-inflammatory activity (Yang et al., 2012); exhibits immunoregulatory, anti-ulcer, gastroprotective (Astudillo et al., 2002) and hepatoprotective activities (Valchalkova et al., 2004), antitumor effect on HCT 15 (Li et al., 2002); it inhibits tumors related to skin in mice (Oguru et al., 1998); acts as a protective agent against hepatotoxicants and treats hepatitis (Liu et al., 1993).

74.2.3 SQUALENE

Squalene possess chemopreventive activity against colon carcinogenesis (suppresses ACF formation and crypt multiplicity; Rao et al., 1998); acts as cardioprotective agent (Farvin et al., 2006); inhibits the proliferation of breast cancer cells (Loganathan et al., 2013); therapeutic and the ability to deter tumor regression and promotion (Desai et al., 1996).

74.2.4 β-SITOSTEROL

β-Sitosterol has growth inhibiting effects on adenocarcinoma cells called MDA-MB-231 and MCF-7 which are breast cancer cells of humans (Awad et al., 2007). Jayaprakasha et al. in 2007 identified that this compound effectively cures benign prostatic hyperplasia (BPH); it attenuates β-catenin and PCNA expression and also quenches the free radicals in *in-vitro* hence it is a possible anticancer treatment for colon cancer (Baskar et al., 2010); reduces the uptake of cholesterol into the intestine by inhibiting the expression of NPC1L1 in enterocytes (Jesch et al., 2009); induces apoptosis in MCA-102 murine fibrosarcoma cells by activating ERK and downregulating Akt (Moon et al., 2007).

74.2.5 CHLOROPHYLL A

Chlorophyll-a and its derivatives are known for their therapeutic purposes and used in traditional medicine (Edwards et al., 1954). In 1997, Hardwick et al. discussed the role of dietary chlorophyll on absorption, digestion, and cancer inhibition activity. The derivatives of natural chlorophyll have various other properties such as anti-inflammatory (Larato et al., 1970), wound healing (Kephart et al., 1955), restricts crystals of calcium oxalate (Tawashi et al., 1980). In photodynamic cancer treatment, it is an important agent (Henderson et al., 1997; Sternberg et al., 1998; Nourse et al., 1988) and in humans, it has chemopreventive properties (Egner et al., 2003).

74.2.6 α-AMYRIN ACETATE

Anticonvulsant, anxiolytic, and sedative effects were found in α-Amyrin acetate and β-Amyrin acetate (Aragão et al., 2009); and anti-inflammatory properties in α-amyrin acetate (Okoye et al., 2014).

74.3 PHARMACOLOGICAL ACTIVITIES

74.3.1 CYTOTOXICITY AND ANTIPROLIFERATIVE ACTIVITY

Mariquit et al. (2018) evaluated antiproliferative activities of oleanolic acid and ursolic acid in 1:1 and 1:2 ratio, chlorophyll a, squalene, α-amyrin acetate and wrightiadione isolated from the leaves and twigs of *W. pubescens* with DCM (Ragasa et al., 2014b, 2015). They used *in vitro* PrestoBlue cell viability assay against cancer cell lines related to humans, namely colon (HT-29 and HCT-116), breast (MCF-7), and a human normal cell line, which is HDFn. They found strongest antiproliferative response of ursolic acid and oleanolic acid (1:1) and (1:2); oleanolic acid, squalene, chlorophyll a, wrightiadione, and α-amyrin acetate against the HT-29 cells followed by HCT-116, and least antiproliferative response in MCF-7 breast cancer cell lines. Additionally, they observed that the cytotoxic activities of normal cell lines HDFn are prevented by these samples.

Chen et al. (2017) evaluated cytotoxic activities of 1–12 (details mentioned under bioactive compounds) identified compounds from the soluble part of ethyl acetate (EAE) (75% ethanol) root extract of *W. pubescens*, using MTT method *in vitro*. They found compound 4, i.e., mollugin exhibited IC_{50} of 8.0 mg/L against HepG2 cells with respect to the cytotoxic activity and the IC_{50}

of 14.7 and 18.2 mg/L with MCF-7 and HepG2 cells, respectively by another compound 11, i.e., ursonic acid.

Bugayong and Jacinto in 2017 from the Philippines assessed the cytotoxic activity of crude extracts of *Wrightia pubescens*, against certain types of cancer which belongs to humans, and they are named as follows HCT 116 (colorectal cancer cell line) and A549 (adenocarcinoma cell line) using MTT assay. They reported cytotoxic activities against HCT116 and A549.

Zuhrotun et al. (2017) tested the cytotoxicity of MEs of *W. pubesens* against *Artemia salina* L. using Brine Shrimp Lethality bioassay along with 3 species of Simaroubaceae, 16 species of Apocynaceae, and 2 species of Magnoliaceae from Indonesia. They found *Artemia salina* L. (LC_{50} < 1,000 µg/ml) is prone to toxicity when treated with *W. pubesens* ME.

74.3.2 ANTI-INFLAMMATORY AND ANTINOCICEPTION

In RAW 264.7 murine macrophages, Jittimanee et al. (2013) observed inhibitory activity of *W. pubescens* latex on prostaglandin E2 (PGE2) synthesis and cyclooxygenase 2 (COX-2) protein expression and concluded that they are responsible for the plant's anti-inflammatory and antinociceptive qualities (Ragasa et al., 2014b) and reduced inflammation and pain.

74.3.3 ANTIOXIDANT ACTIVITY

Traxler et al. (2021) isolated and identified tryptanthrin (6) and kelampayoside A (7) in the methanolic stem bark extract of *W. pubescens*. They tested the radical scavenging activities of these isolated compounds which are considered specialized metabolites from indolic and polyphenolic biosynthetic pathways and crude methanolic extracts. The results indicated that tryptanthrin and kelampoyoside did not show any antioxidative properties.

74.4 CONCLUSIONS AND FUTURE PROSPECTS

Wrightia. pubescens R.Br. is an important medicinal plant, used to treat different diseases like osteoarthritis, acute upper respiratory infection, intractable hiccups, malaria, scrofula rheumatic arthralgia and dysentery due to its pharmacological properties of bioactive compounds. In this plant, some of the bioactives like β-sitosterol, ursolic acid, oleanolic acid, squalene,

α-Amyrin acetate, wrightiadone, etc., were reported from the leaves and twigs. Tryptanthrin, an indole derived compound and a phenolic apio glucoside named kelampoyaside A are extracted from stem bark. Coumarin, 4-hydroxybenzoic acid, ursonic acid, β-sitosterol, medioresinol, mollugin, 4-hydroxymethyl-5-hydroxy-2H-pyran-2-one, vanillin, β-daucosterol, cleomiscosin B, scopolectin, and vanillic acid are extracted, isolated, characterized, and identified from the roots. However, bioactives can also be isolated and characterized further from the flowers, seeds, callus, and other tissues to assess whether they are able to report the same compounds. Similarly, many of their biological activities can be studied. If individual compounds are isolated and tested for their therapeutic activities, we may find new drug lead compounds which help in the treatment of human alignments and drug discovery by the pharmaceutical industry.

KEYWORDS

- **bioactive compounds**
- **cyclooxygenase 2**
- **cytotoxicity**
- **oleanolic acid**
- **prostaglandin E2**
- ***Wrightia pubescens***

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CHAPTER 75

Bioactive Compounds and Pharmacological Properties of *Cipadessa baccifera* (Roth) Miq.

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75.1 INTRODUCTION

Cipadessa baccifera (Roth) Miq., also known as Ranabali, belongs to the Meliaceae family. It is synonymously known as *Cipadessa cinerascens*, *Cipadessa fruticosa, Mallea integerrima*, or *Ekebergia indica*. In Marathi, it is known as Ranabili; in Kannada, Narsullu, Bettada Bevu; in Malayalam, Kaipanarangi; in Tamil, Puilipancheddi; in Hindi, Nalbila, and in Telugu, Adavikarivepa. It is a bushy shrub with small flowers and pinnate leaves. The flowers of *Cipadessa* are isomerous, hypogynous, and arranged with six whorls; sepals have marginal veins, the ovary is syncarpous and has five locular structures. *Cipadessa* is primarily found in laterite hills, village areas, dry forests, hilly places higher than 400 ft. In the Indian subcontinent, the species is spread across India, Bhutan, Nepal, and Sri Lanka. In Indochina, it is spread through Laos, Vietnam, Thailand, Myanmar, and Cambodia. In the Malesian biogeographical region, the plant species is spread across Malaysia, the Philippines, and Indonesia. The plant leaves and fruits are used to feed cattle, toothbrushes, and wood for fuel. It was tested and concluded that it helps relieve diabetes, piles, food poison, and severe headache (Roy and Saraf, 2006). Limonoids in *Cipadessa baccifera* reported pharmacological activities like antibacterial, antifungal,

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antimalarial, antitumor activities on insects and humans (Roy and Saraf, 2006). *"Ya Luo Qing"* is folkore medicine from *Cipadessa baccifera* used in China, Xishuangbanna, to treat some the diseases like itchy skin, rheumatism, burns, scalds, dysentery, and malaria. Roots and leaves of *Cipadessa* species are used to prepare the folk medicine used by Doi people present in the southwest part of China (Lin et al., 2008). A mixture of stem bark paste, juice of leaves and goat milk is used to treat wounds and injuries (Ram et al., 2004). The ethnobotanical study conducted on *Cipadessa baccifera* reported that leaves have medicinal value that helps to treat the snake bite, dysentery, and urine stone. The leaves, roots, and bark of *Cipadessa baccifera* help cure psoriasis disease (Ayyanar and Ignacimuthu, 2005). The plant is used for the treatment of poisonous snake bites by the tribals of Paliyar in Pachalur hills, India (Ganesan et al., 2004). Macerated green leaves, blended with gingelly oil, applied over the skin ailments, can relieve the diseases (Bhakshu et al., 2016).

75.2 BIOACTIVES

Limonoids and terpenoids present in *Cipadessa baccifera* are used for medicinal purposes. The analysis of methanolic leaf extract of *Cipadessa baccifera* through GCMS revealed the 17 bioactive compounds. Significant compounds are sclareloxide, phytol, hexadecanoic acid, and minor compounds such as squalene, hepta triacontanol, lauric anhydride octadecanoic acid, pentadecanoic acid, pentamethyl, trimethyl (Jeevitha et al., 2018). The term "limonoids" came from the tartness of citrus fruits, especially lemon fruit. Structurally, limonoids forms due to the lack of four-terminal carbons of the rear chain in the apoeuphane or apotirucallane frame and are cyclized to create the 17β-furan loop. Consequently, limonoids are further recognized as tetranortriterpenoids (Tan and Luo, 2011). Limonoids are modifications of triterpenoids with a prototypical structure commonly present in the Meliaceae family (Liao et al., 2009). Around 19 compounds, include seven analogs, were found, and 12 limonoid compounds were found by the Silica gel chromatography method. The analog compounds such as Rugeanin A and Febrifugin A (Leite et al., 2005), 2`S-cipadesin (Gan et al., 2007), granatumin E (Liao et al., 2009), febrifugin (Luo et al., 2000), Khaysin T (Cao et al., 2020), Cipafren M (Siva et al., 2014) were reported. Their limonoid structures were found by EDC Calculation and analysis of extensive spectroscopy.

Some compounds have cytotoxic, antifungal, and nematocidal activities (Liao et al., 2009). The leaves of *Cipadessa baccifera* contain 41 essential oils (EOs) found through gas chromatography-mass spectrometry (GC-MS). EOs are a mixture of 20 to 60 various concentration compounds. Major EOs present are isoledene, beta-sesquiphellandrene, caryophyllene, 1S cis-calamenene, bicyclononane, and Trimethyl-4-vinyl (Kavitha et al., 2016). The outcomes revealed that the methanolic leaf infusion of *C. baccifera* (CB) included flavonoids, alkaloids, steroids, saponins and tannins. The LC-MS/MS analysis intimated that this fraction included kaempferol 3-0-β-D-glucopyranoside, quercimeritrin, glehlinoside B and oxofangchirine (Lubis et al., 2021).

To date, various classes of compounds are isolated from *C. baccifera.* The consolidated list of compounds are given as follows: The tetranortriterpenoids (limonoids) isolated from *C. baccifera* are Cipadesin are (2′R)-Cipadesin, (2′S)-Cipadesin, Methyl 3β-(isobutanoyloxy)-1-oxomeliac-8,30-enate, febrifugin, 10-[(2R)-2-Methyl butanoyl] proceranolide, 10-[(2S)-2-Methyl-butanoyl] proceranolide, 3β-(Isobutyryloxy) mexicanolide, Tigloylseneganolide A, Swietemahonolide, Cipadesin A, (2′R)-Cipadesin A, (2′S)-Cipadesin A, Cipadesin B, Cipadesin E, Cipadesin J, K, L, M, N, O, P, and Q, Cipadonoid A and B, Cipatrijugin D, E, and F, Mombasol, and Rubralin. The sesquiterpenoids isolated from *C. baccifera* are Bacciferin A, Bacciferin B, 9β-Hydroxyaphanamol II, Guaianediol, Cryptomeridiol, Eudesm-4(14)-ene-1β,6α-diol, Eudesm-4(14)-ene-3α,11-diol, Eudesm-4(14)-ene-8α,11-diol, and Aromadendrane-4β,10α-diol. The steroid compounds separated from the plant are as follows: (6β)-6-Hydroxystigmast-4-en-3-one (3β,5α,8α)-5,8-Epidioxyergosta-6,22-dien-3-ol, (17α,20R)-17,20-Dihydroxypregnane-3,16-dione, (2β,3β,4β)-2,3,4-Trihydroxypregnan-16-one, (2β,3β,4β)-2-Acetoxy-3,4-dihydroxypregnan-16-one, (2α,3α,4β)-2,3,4-Trihydroxypregnan-16-one, Meliavosin, (2β,3β,5α)-2,3-Dihydroxypregnan-16-one and (3β,5α,16α,17β)-17-Ethyl-10-methylgonane-3,13,16-triol. The other compounds isolated are as follows: 1,4-Epoxy-16-hydroxyhenicosa-1,3,12,14-tetraene, 1,4-Epoxy-16-hydroxyhenicosa-1,3,12,14,18-pentaene, (-)-9′-O-(E)-Coumarate-5,5′-dimethoxylariciresinol and (+)-9′-O-(E)-Feruloyl-5,5′-dimethoxylariciresinol (Bandi and Lee, 2012). The chemical structures of few bioactive compounds of *C. baccifera* are given in Figure 75.1.

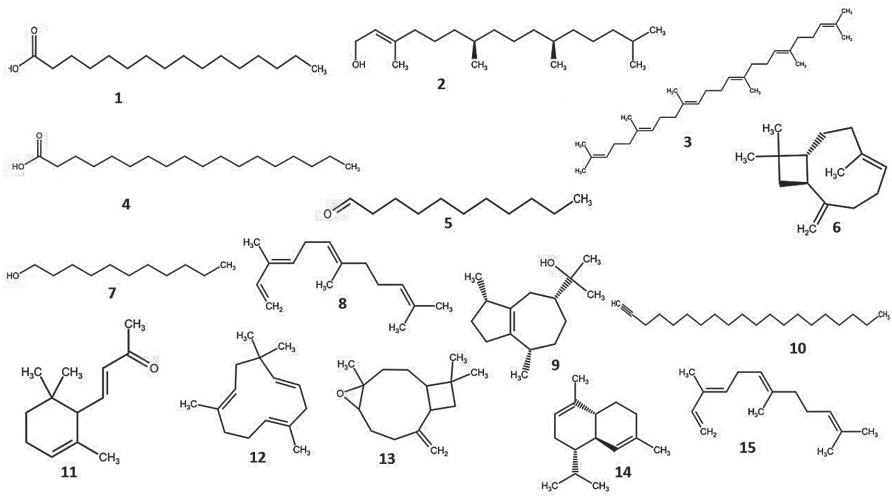


FIGURE 75.1 The chemical structures of few bioactive compounds of *C. baccifera* are: (1) hexadecenoic acid; (2) phytol; (3) squalene; (4) octadecanoic acid; (5) hendecanal; (6) caryophyllene; (7) undecanol; (8) farnesene; (9) guaiol; (10) eicosyne; (11) ionone; (12) humulene; (13) caryophyllene oxide; (14) cadinene; and (15) farnesene.

Source: Chem4Word 2020, Release 9 – (3.1.19.7810) tool was used to draw chemical structures.

75.3 PHARMACOLOGY

75.3.1 ANTIOXIDANT ACTIVITY

Flavonoids hold antioxidant characteristics that restrain oxidoreductase enzyme actions, viz, xanthine oxidase, and play a substantial part in uric acid biosynthesis. An investigation was intended to ascertain the antioxidant action and xanthine oxidase repression in methanolic leaf extract of *Cipadessa baccifera.* The outcomes revealed that the ethyl acetate (EAE) leaf fraction of *C. baccifera* fraction had xanthine oxidase repression action, remarkable content of flavonoids, and possessed antioxidant activity (Lubis et al., 2021). In an experiment, four distinct approaches were used to assess the antioxidant capability of the distillations of the three fruit extracts via ferric reducing/antioxidant power assay (FRAP assay), DPPH free radical-scavenging analysis, metal chelating assay and reducing power assay. The antioxidant potential of fruit extracts from different solvent extraction systems using FRAP and DPPH assay indicated that *C. baccifera* possesses DPPH inhibition percentage as 40.21% for aqueous; 44.24% for aqueous

methanolic; 53.19% for ethanolic, and 51.20% for acetone extracts. In FRAP assay, *C. baccifera* plant extracts exhibited 9873.56±0.351, 14181.03±0.702, 9381.26±0.208, and 12234.63±0.251 (μM AAE/g fresh weight) for aqueous, methanolic, ethanolic, and acetone solvents, respectively. The antioxidant capacity of fruit extract obtained for *C. baccifera* possesses in different solvent extraction systems using reducing power, and metal chelating assays revealed 0.085±0.002, 0.123±0.003, 0.054±0.001 and 0.087±0.002 (μM AAE/g fresh weight) for aqueous, methanolic, ethanolic, and acetone solvents, respectively. The metal chelating was highest in EE (55.59%), followed by hydro-extract (48.45%), methanolic (43.21%) and acetone extract (42.38%). In conclusion, the antioxidant potential of extract differs in its capacity to respond to biologically dangerous free radicals (Valvi et al., 2011). In an experiment, the complete phenolic content in the defatted ethanolic extract (DEF) of *C. baccifera* (CB) remained higher than all other essences, 389.2 mg gal/l. The ethanolic extract (EE) conferred lower entire phenolic content than DEF, 383.5 mg gal/l. CB's hydro defatted extract (HDE) conferred better total phenolic content than hydro extract (HE) 136.6 mg gal/l and 121.55 mg gal/l, respectively. The above result found that the DEF of CB leaf extracts displayed more DPPH radical interference than other extracts (Murkute and Shinde, 2019).

75.3.2 ANTI-MICROBIAL ACTIVITY

Using the well diffusion assay, four separate infusions of *C. baccifera* were evaluated for their antimicrobial activity against *S. aureus* and *E. coli*. The strength of 160 mg/ml and 140 mg/ml of the EE conferred a zone of inhibition 1.05 cm and 0.95 cm, respectively, compared to the approved antibiotic chloramphenicol toward *E. coli*. The ethanolic defatted extract recorded a zone of inhibition of 1.05 cm and 1.15 cm at the strength of 160 mg/ml and 140 mg/ml, respectively, toward *E. coli* (Murkute and Shinde, 2019). *Cipadessa baccifera* plant crude extract has effective antimicrobial activity against *Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhi, Shigella flexneri,* and *Vibrio cholerae.* Amongst the four crude solvent distillations examined, the chloroform solvent extract was efficient even at a modest 5% concentration. Besides, investigation of the $CHCl_3$ distillation produced six fractions; fraction of four restrained microbes (5–7 mm) upon five pathogens examined, excluding *S. aureus*. Gentamicin disc at a concentration of 10 mg, used as a standard (Malarvannan et al., 2009).

Multi-drug-resistant bacteria cause severe damage to human beings, challenging to control because of their strains. However, the screening of *C. baccifera* leaf extract shows that it has efficient antimicrobial activity against multi-drug-resistant pathogenic bacteria. It can be used for many biomedical applications soon (Bhakshu et al., 2016).

75.3.3 ANTI-DIABETIC AND WOUND HEALING ACTIVITY

In an experiment to study the wound healing activity of *C. baccifera* extracts in alloxan-mediated diabetic models, the rat models were jabbed with a sole measure of Alloxan monohydrate (120 mg/kg, BW) intraperitoneally through routine saline. The excision was carried out as per the method (Tuhin et al., 2017). The incision pattern was executed (Mugade et al., 2017). On the 16th day, the 200 mg/kg EE administered group registered 95% scar closing, whereas 100 mg/kg administered showed 75% scar closing. In histological observation, excised skin prescribed with EE of CB revealed multifocal average lymphocytic infiltration and epithelial hyperplasia at the dermis, inferring wound healing. Tensile power of dermis increased in the ethanol extract-treated CB group as associated with the standard. In the 200 mg/kg treated group, 60.3% tensile power was observed. An improvement in tensile power of the skin may be associated with keratin accumulation in the injury. Incised skin administered with CB revealed recently developed epithelium (epithelization), fibroblasts generation in the dermis and average focal ablation of the exterior epithelium (Murkute and Shinde, 2019).

75.3.4 OVICIDAL ACTIVITY

Culex quinquefasciatus is a vector for filariasis and arboviruses. Filariasis is a significant common wellness predicament and is a challenging socio-economic difficulty in many tropic nations. Pesticide resistance amongst mosquito vectors for artificial pesticides continues to be a significant obstacle for restraint efforts. An investigation estimated the ovicidal capability of crude infusions from *Cipadessa baccifera* to the standard insect growth regulators (IGR) on freshly deposited eggs of *C. quinquefasciatus*. The percent egg-hatching impediment was inversely proportionate to the concentration of *Cipadessa baccifera* infusions. The malformation and damage to the eggs were observed. Acetone infusions recorded significantly higher ovicidal action, and variations in shell phenotype on the cells were

witnessed. The highest ovicidal action was in acetone infusions with a DT_{50} value of 1.70 hrs. (0.91–2.22). In conclusion, the extracts of *C. baccifera* can be utilized as an ovicidal factor for restraining mosquito groups in earlier stages (Ramkumar et al., 2019).

75.3.5 CYTOTOXIC AND ANTI-CANCER ACTIVITY

Eight limonoids isolated from *C. baccifera*, cipadesins J, K, L, M, N, O, P, and Q, revealed cytotoxic action upon five carcinoma cell lines, including SMMC-7721 (hepatocellular carcinoma), HL-60 (myeloid leukemia), SW480 (colorectal cancer), MCF-7 (breast cancer) and A-549 (lung cancer) and were assessed by MTT experiment (11) with DDP (cis-diammineplatinum (II) dichloride) as positive control. Amongst them, cipadesins K and N displayed average cytotoxicity toward HL-60 cells with IC_{50} of 20 mm; compound cipadesin K exhibited faint toxicity toward SMMC-7721 cells (IC_{50} 36.5 mm), whereas the other compounds were dormant (Ning et al., 2010). Cipatrijugins D and A and cipatrijugins F and E separated from *C. baccifera* stem bark were assessed for their cytotoxicity towards A-549, SMMC-7721, HL-60, SW480, and MCF7 human tumor cell lines through *in vitro* assays (MTT) with DDP as a positive standard (Monks et al., 1991). Cipatrijugin E, which holds the C(3)¼O group, revealed significant dosage-reliant restraint against the SMMC-7721 (IC_{50} 21.6), HL-60 (IC_{50} 4.5), SW480 (IC_{50} 6.6) and MCF-7 (IC_{50} 5.0) cell lines. In contrast, other compounds displayed no repressive actions. The anticancer activity of *Cipadessa baccifera* was estimated by exposing MFC-7, EAC, and H-29 Cell lines to the extract for 24 hours. MTT Assay is used to check the viability of cells. In the phosphomolybdate experiment, *C. baccifera* distillation exhibited excellent antioxidant action (IC_{50} = 0.42 mg/ml), comparable to the standard ferulic acid (IC_{50} = 0.22 mg/ml). The complete phenolic content existing in the methanolic extract of *C. baccifera* was 338.38 mg Gallic acid equivalents per liter. *Cipadessa baccifera* conferred more favorable cytotoxicity toward HT-29 cell lines (IC_{50} = 1.86 mg/ml) and EAC (IC_{50} = 4.22 mg/ml) opposed to MCF-7 cell lines (IC_{50} = 34.28 mg/ml). The infusion conferred excellent ROS mitigating and anticancer activity against EAC, and HT-29 cell lines. Nevertheless, the action was weakly associated with the control. *Cipadessa baccifera* extract displayed negligible cytotoxic effect toward MCF-7 cell lines (Rajani et al., 2015).

75.3.6 ACETYLOLINESTERASE INHIBITORY ACTIVITY

Around 12 earlier un-explored mexicanolide-type limonoids, inclusive of two pairs of isomers, synchronically with seven familiar analogs, were separated from *Cipadessa baccifera*. Structural alterations essentially happened at the attachment of the carbon residues and C-3 associated with C-17. 3-*O*-detigloyl-3-*O*-isobutyryl-21-deoxo-23-oxofebrifugin A and 21-deoxo-23-oxofebrifugin A are rare, naturally occurring mexicanolide-type limonoids displaying an *α*,*β*-unsaturated-*γ*-lactone motif at C-17. Besides, cipaferen R is the principal degraded tetranortriterpenoid, highlighting an acetyl group at C-17 (Cao et al., 2020). Febrifugin A, 3-*O*-detigloyl-3-*O*-isobutyrylfebrifugin A, khaysin T and febrifugin displayed mild cytotoxic action upon the tested cells. Granatumin E, 3-*O*-detigloyl-3-*O*-isobutyrylfebrifugin A, 2′*S*-cipadesin A and khaysin T revealed mild inhibitory actions upon acetylcholinesterase (AChE, 50 μM) (Cao et al., 2020).

75.3.7 ANTI-LEISHMANIASIS ACTIVITY

Leishmaniasis includes a combination of torrid infections provoked by various hemoflagellate protozoan parasitoids of the genus *Leishmania* and spread zoonotically by the winged insects (female) of the genus *Lutzomyia* and *Phlebotomus*. The WHO has adopted the different signs of the condition as the source for classifying leishmaniasis into visceral, cutaneous, and mucocutaneous; in all of its three clinical patterns; it continues a significant known health predicament in the subtropical and tropical regions of the world (Ambrozin et al., 2005). In the scarce availability of anti-Leishmania vaccines, chemotherapy persists as the aid for tackling this infection (Davis et al., 2004). However, the practice is though potent, deadly antimonials (pentavalent), viz, Pentostam® (sodium stibogluconate) and Glucantime® (meglumine antimoniate) need to be injected everyday intramuscularly, creating repulsive side effects. Additionally, these medications are costly and not consistently efficient (Olliaro and Bryceson, 1993). Parasites of the genus *Leishmania* harbor three enzymes associated with the recycling of nucleotides (purine), hypoxanthine-guanine phosphoribosyltransferase (HGPRT), xanthine phosphoribosyltransferase (XPRT) and adenine phosphoribosyltransferase (APRT) (Ullman and Carter, 1997). APRT catalyzes the a-d-5-phosphoribosyl-1-pyrophosphate (PRPP) and adenine, resulting in pyrophosphate (PPi) and adenosine-5-monophosphate (AMP) (Musick, 1981).

Meliaceae plant extracts of various species, including *C. baccifera*, were examined for anti-Leishmania activity spectrophotometrically. Various solvent extracts from different plant parts of *Cipadessa baccifera* inhibited the ARPT enzyme from *Leishmania donovani* significantly. The dichloromethane (DCM) and ME of fruit inhibited the ARPT enzyme to the tune of 63.6% and 78.7%, respectively; the hexane, DCM, and ME of branches inhibited the ARPT enzyme to the tune of 70.1%, 61.0%, and 90.8%, respectively; the hexane, DCM, and ME of leaves inhibited the ARPT enzyme to the tune of 65.1%, 56.4%, and 90.3%, respectively (Ambrozin et al., 2005).

75.3.8 ANTI-TRYPANOSOMIASIS ACTIVITY

Trypanosoma cruzi, a protozoan is a causal organism for Chagas' disease that troubles some 1.6–1.8 crores individuals, mainly from Central and South America; around 25% of the population in that region is at a danger of infection (WHO, 2021). Managing the pest (*Triatoma infestans*), vector in endemic zones has almost practically eliminated the disease transmission through insect stings. Consequently, congenital transmission and blood transfusion are the significant reasons for the disease spreading (Coura and De Castro, 2002). Its therapy is a hurdle as the unique medication available commercially is benznidazole has substantial aftermath after the treatment (De Castro, 1993).

The *C. baccifera* plant parts (leaves, fruits, stems, and roots) were homogenized separately and extracted with hexane, DCM and methanol (thrice) at 37°C. The extracts collected were examined on gGAPDH enzyme from *T. cruzi*. Vacuum liquid chromatography with silica gel utilizing a hexane-DCM-ethyl acetate (EAE)-methanol gradient resulted in 9 fractions. Column chromatography on silica gel of fraction 3 and 6 yielded 3 compounds viz, 7-methoxyflavone (**1**), 3′,4′,5′,5,7-pentamethoxyflavone (**2**) and flavone (**3**). Compound (**3**) exhibited potent inhibitory action towards gGAPDH. The inhibitory activity of the compound (**1**) at a concentration of 450 microMol/L was 9.7%; Compound (**2**) was 78.3% (397 microMol/L), and for compound (3), it was 100% (268 microMol/L). The crude extracts of hexane, DCM, and methanol of *C. baccifera* of exhibited maximum inhibitory activity as follows: fruit methanolic extract (100 micrograms/ml) inhibited 84.8% of gGAPDH; branch hexane and methanolic extract (100 micrograms/ml) inhibited 98.3% and 90.2% of gGAPDH, respectively; leaves methanolic extract inhibited 66.7% of gGAPDH enzyme. Hence, the examined

compounds from *C. baccifera* could be recognized as an encouraging source of potent compounds to treat Chagas' disease (Leite et al., 2009).

A study examined the trypanocidal activity of limonoids and flavonoids separated from several plant parts of *C. baccifera.* The mexicanolide limonoids 3–6, separated from fruits of *C. baccifera* (dichloro-methane), revealed notable trypanocidal action on trypomastigotes of *Trypanosoma cruzi*. The compounds isolated were mexicanolide (IC_{50} = 326.3 µmol/L), cipadesin (IC_{50} = 189.0 µmol/L), cipadesin A (IC_{50} = 136.1 µmol/L) and febrifugin (IC_{50} = 168.0 µmol/L) and the standard control Gential violet (76.0%). The percentage of inhibition at 250 µg/mL towards trypomastigotes recorded were cipadesin (80.81 ± 4.1%), febrifugin (65.69 ± 2.9), mexicanolide (77.21 ± 2.5), and cipadesin A (88.95 ± 2.9) and for the standard control gentian violet (100.0 ± 0.0%) (Leite et al., 2010).

75.3.9 ANTI-CANDIDIASIS ACTIVITY

Candida albicans are opportunistic microbial pathogens of genital and oral diseases in human beings, resulting in a fatality in immuno-compromised sufferers (e.g., cancer chemotherapy, AIDS, bone marrow or organ transplantation). It is often seen in the gastrointestinal tract and oral cavity, seldom causing adverse consequences, although its excessive growth leads to candidiasis in HIV cases. *Candida* plagues of the vagina, skin or mouth happen due to antibiotic medication that suppresses helpful and pathogenic microorganisms allowing *Candida* to proliferate, ending in "yeast" infection or fungemia or candidiasis (moniliasis) (Ryan and Ray, 2018) Extraordinary levels of anti-fungal medication immunity have been notified in *Candida* species that displayed resistance upon currently available antibiotics, namely, fluconazole ketoconazole and 5-flucytosine (5-FU) (Hajjeh et al., 2004). *C. baccifera* samples were extracted first with petroleum ether and followed by EAE and ethanol. Sterile discs soaked in the extracts (1 mg/mL) for 24 h. The discs, infused with extracts, were appropriately dried and used. *Candida albicans* MTCC181 was inoculated in Petri dishes with nutrient agar. The discs comprising plant infusions were set on the media containing plate surface (0.1 mL of culture (5 × 105 CFU/mL) of *C. albicans,* kept for a day at 30°C. Approved antibiotics, fluconazole, and kanamycin, served as standard controls. The PE and EAE leaf extracts' zone of inhibition were 18 and 12 mm, respectively. The MIC values observed were 250 and 500 micrograms per mL for the leaf extract, which proved the anti-candidiasis activity of *C. baccifera* extracts (Bhakshu et al., 2016).

KEYWORDS

- **anticancer activity**
- **antioxidant activity**
- **bioactives**
- **candidiasis**
- ***Cipadessa baccifera***
- **insect growth regulators**

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CHAPTER 76

An Overview of Bioactive Constituents and Pharmacological Actions of Red Quinine (*Cinchona pubescens* Vahl) and Quina (*Cinchona calisaya* Wedd.)

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76.1 INTRODUCTION

Cinchona pubescens Vahl is considered to be the most economically important plant species after *Coffea* in the Rubiaceae family. As *Cinchona pubescens* bark and roots contain quinine, it is grown in some of the World's tropical areas (Jäger, 2004). *C. pubescens* is called differently in various parts of the World. In English, it is called red Cinchona, in Dutch kinaboom, in Indonesia as Kina, in French as quinquina jaune, quinquina, in Portuguese as quinquina, in Malay as kuinin and in Spanish, it is known as quino. All cinchonas are inherent to the Amazonian region of the Andes (eastern slopes) on both sides of the equator (from Bolivia to Columbia); they are also spread towards the northern section of the Andes (Jäger, 2015). They are commonly called: Quinine tree, quinine, quinoa, red Cinchona. *Cinchona pubescens*, is now grown in different tropical regions to produce quinine (obtained from the root and bark of the tree), a compound used to treat malaria or jungle fever. The red quinine tree has been perceived as a natural weed in the National Park of Galapagos for 30 years (Buddenhagen et al., 2004).

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Cinchona pubescens is an evergreen tree (10 to 25 m) with pink or white fragrant flowers organized in clusters. The leaves of *C. pubescens* are broad, seldom sub-orbicular or elliptic-ovate, of 20–25 cm lengthier; 18 to 45 cm broad, dorsally puberulent, or glabrate, petioles (1.5–4.5 cm), caducous, and ovate stipules. Fruit (1–4 cm), oblong to lanceoloid capsules carrying 50–55 seeds, base to apex dehiscent. Seeds have a prominent ciliate wing, and seeds are 5–6 mm long by 1 mm. During the 17th century, different varieties of the *Cinchona* were used as a conventional therapy against jungle fever (malaria) due to the presence of quinine. It has been a cure for malarial fever for over 350 years, though antimalarial activities of various alkaloids have been found in its bark (Canales et al., 2020).

Cinchona calisaya Wedd. (Common name: quina) which belongs to the Rubiaceae family is a medicinal plant endemic to South America in the Southern Andes Forest. It is widely spread in Cameroon, India, Vietnam, and Java, and in some other African and Asian countries. The seeds of *Cinchona calisaya* growing on mountains in Bolivia were collected with much difficulty in the 1860s, and the Dutch plantations had a remarkable reversal of fortune (Bruce-Chwatt, 1990). Cinchona was first grown in the Cibodas area (West Java) after being introduced to Indonesia from Bolivia. As a result of plantation or cultivation, in India, it is mainly found in the hilly regions. Indonesia tops all throughout the World in the production of Quina plants (Hidayat et al., 2016). Varying amounts of alkaloids are present in *C. calisaya* which is one of the 26 species of *Cinchona* trees known to date. *C. calisaya* trees thrive as single trees or in clusters of a few trees, and in many historical sites no longer have *C. calisaya* trees because of overharvesting and deforestation. Because of their wide-ranging activity of alkaloids present in the plant, alkaloids are termed multiple-purpose defense substances (Ruiz-Mesia et al., 2005). Several diseases are treated with the help of drugs from Cinchona alkaloids (Shibuya et al., 2003). The anti-inflammatory effects were highest in *Cinchona pubescens* bark extract (Schink et al., 2018). It is a tonic, anti-fever, and digestive stimulant in addition to being an antimalarial drug. General fatigue, gastrointestinal disorders, anemia, appetite stimulant, fevers, and indigestion are all treated with the bark extract (Olafson et al., 2017).

76.2 BIOACTIVES

The alkaloid quinine is frequently considered the common constituent of cinchona bark; the three additional alkaloids; quinidine, cinchonine, and cinchonidine are generally present (Martin and Gandara, 1945). By

spectroscopic methods, 12 compounds were isolated in sufficient amounts from C*inchona pubescens* callus, the seven known anthraquinones identified are, anthragallol-1,2-dimethylether, alizarin-2-methylether, purpurin-1-methylether, purpurin, 2-hydroxy-1,3,4-trimethoxy-anthraquinone 1-hydroxy-2-hydroxy-methyl-anthraquinone, and 2,5-(or 3,5-) dihydroxy-1,3,4-(or-1,2,4-) trimethoxy-anthraquinone. The five new anthraquinones identified in *C. pubescens,* which were not found in other plants 1,6-(or 1,7-)dihydroxy-2-methylanthraquinone, 2-hydroxy-1,3,4,6-(or -1,3,4,7-) tetramethoxyanthraquinone, 4,6-(or 4,7)-dihydroxy-2,7-(or -2,6-)dimethoxyanthraquinone, 5-hydroxy-purpurin-1-methylether, and 6,7-dihydroxy-1-methoxy-2-methylanthraquinone have been separated (Wijnsma et al., 1986).

The alkaloids identified in the extracts of stems and leaves of *Cinchona pubescens* are as follows: Cinchonine, Cinchonidine, Quinine, Quinidine, Dihydro-cinchonidine, Dihydroquinine, Dihydro-quinidine, Cinchonamine, 10-Methoxy-cinchonamine, Quinamine, 3α,17β-Cinchophylline, 3α,17α-Cinchophylline, Cinchoninone/quinidinone. The anthraquinones identified in *C. pubescens* are 1,8-dihydroxy anthraquinone, 1-hydroxy-2-hydroxy methyl anthraquinone alizarin-1-methyl ether, alizarin, and rubiadin (Mulder-Krieger et al., 1984). The flavonoids apigenin (4′,5,7-trihydroxy flavone), quercetin, catechin, and kaempferol were identified from of *Cinchona pubescens* (Noriega et al., 2015). Norharman was the most abundant alkaloid, along with indole-3-aldehyde and 4-hydroxy methyl quinoline (Robins et al., 1987). TLC has been used to identify heterocyclic alkaloids and quinoline. Due to the presence of quinvic acid, the bark of *Cinchona pubescens* possessed a weak cytotoxic activity (Raffauf et al., 1978).

In *C. calisaya*, there are different pharmacological profiles for the four essential Cinchona alkaloids, namely cinchonine, quinine, cinchonidine, and quinidine. Around 30 minor and less examined alkaloids have been described from *Cinchona calisaya* since the primary isolation of quinine in 1820 (Maldonado et al., 2017). Cinchophyllines are obtained from leaves, whereas barks and leaves are the primary sources of *Cinchona calisaya* alkaloids. An excess of 20 alkaloids containing 15% as a whole, especially cinchonine, quinine, cinchonidine, and quinidine, is found in the bark of *Cinchona calisaya* along with active mixtures like tannins (3–10%). The four essential alkaloids discovered from *C. calisaya* showed variability among samples observed; for this discovery, 22 trees were sampled. Quinine being 6.6 mg g^{-1} (mean), was the most abundant alkaloid ranging from 0.2 to 25.8 mg g^{-1} (<0.1–2.6%). Only two samples with no noticeable degrees of

quinine, practically half of all samples analyzed with yielded 5.0 mg g^{-1} of quinine; the second abundant alkaloid was quinidine showing an average of 2.3 mg g^{-1} (0.2%) across the tests. The samples showed a range of quinidine between 0.1 and 10.0 mg g^{-1}. Even cinchonine showed an average of 2.2 mg g^{-1} (<0.2%). One sample had a very high content of cinchonine (22.9 mg g^{-1}) was found, which fluctuated incredibly like quinine. The mean of cinchonidine was 0.5 mg g^{-1} (<0.1% of bark), making it the least of the four alkaloids. These four alkaloids identified were compared with authentic samples (melting point, spectral comparison, and chromatographic behavior) (Alonso, 2004). Besides these components, the bark contains acids, bases, oils, and minerals, for example, triterpene (quinovic acid), organic (quinic acids), phenols (caffeic acid), flavonoids (proanthocyanidins) phytosterols (Gurung and De, 2017). The compounds present in both *Cinchona pubescens,* and *Cinchona calisaya* are represented in Figure 76.1.

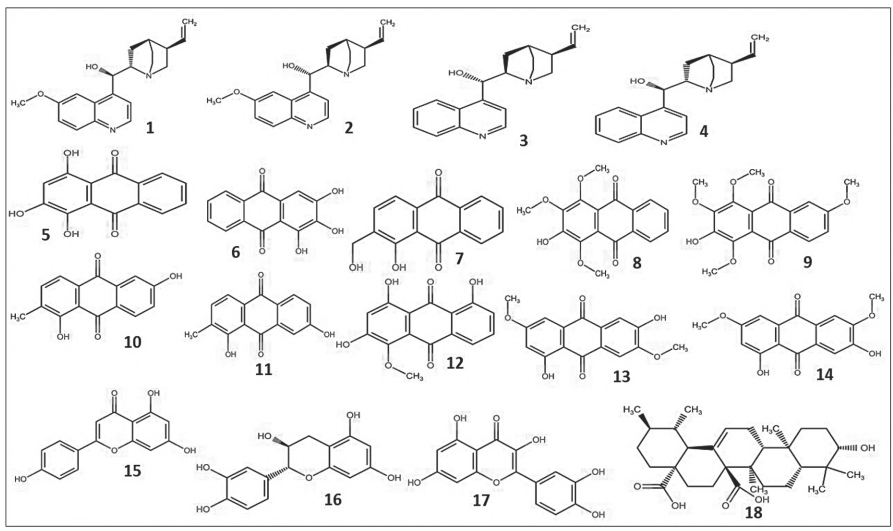


FIGURE 76.1 Common alkaloids present in C*inchona pubsecens* and *Cinchona calisaya:* Quinine (1); quinidine (2); cinchonine (3); cinchonidine (4); anthraquinones present in *Cinchona pubescens:* purpurin-1,2,4-trihydroxyanthraquinone (5); anthragallol (6); 1-hydroxy-2-hydroxyl methyl anthraquinone (7); 2-hydroxy-1,3,4 trimethoxyanthraquinone (8); 2-hydroxy-1,3,4,6-tetra methoxy anthraquinone (9); 1,6 dihydroxy-2-methyl anthraquinone (soranjidiol) (10); 1,7-dihydroxy-2-methyl anthraquinone (11); 1-methoxy-2,4,5-trihydroxy anthraquinone (12); 1,6-dihydroxy-3,7-dimethoxy anthraquinone (13); 1,7-dihydroxy-3,6-dimethoxy anthraquinone (14); flavonoids present in both species: Apigenin (4′,5,7-trihydroxyflavone) (15); quercetin (16); catechin (flavan-3-ol) (17); and quinovic acid (18).

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

76.3 PHARMACOLOGY

76.3.1 ANTI-OBESITY ACTIVITY

Cinchona bark contains Cinchonine ($C_{19}H_{22}N_2O$). Jung et al. (2012) examined whether cinchonine could reduce high lipid diet (HFD) provoked inflammation and adipogenesis in epididymal adipose tissues and examined the possible mechanisms in reducing adipogenesis. Mice administered HFD along with cinchonine (0.05%) for 70 days had visceral lipid in pads (–26%), decreased body-mass increase (–38%), and free fatty acids, triglyceride levels in plasma, blood glucose and total cholesterol (TC) when compared with mice fed with the HFD. Furthermore, there was a significant reversal and downregulation of HFD-induced galanin-mediated signaling molecules and repression in the expression of genes (adipogenic) in mice's fatty tissues (epididymal) mediated by cinchonine. Cinchonine arrested the upregulation of proinflammatory cytokines (HFD-induced) by repressing TLR4-involved signaling events and toll-like-receptor-2 (TLR2) in mice. The study concluded that cinchonine (dietary) could prevent adipogenesis and associated inflammation, thereby avoiding obesity (Jung et al., 2012).

76.3.2 ANTI-PARASITIC ACTIVITY

A study evaluated the inhibitory activity on trypanosomiasis, leishmaniasis, and malaria caused by the parasites *Trypanosoma* sp., *Leishmania* sp., *Plasmodium* sp. sequentially. A group of 16 combinations of bile acids and the alkaloids of Cinchona was prepared by BartoneZard decarboxylation chemical reaction. C-2 position of quinoline nucleus was functionalized by a radical attack of norcholane substituent in four naturally occurring compounds *viz,* Quinidine, Quinine, cinchonidine, and cinchonine. The newly obtained 16 synthetic combinations of compounds were evaluated *in vitro* for their antileishmanial, antiplasmodial, and antitrypanosomal actions and their cell toxicity towards a standard human fibroblast cell line (WI38). Seven hybrid compounds conferred assuring trypanocidal action with IC_{50} values similar to the popular drug suramine. Moreover, all the 16 combinations exhibited antiplasmodial action with an inhibitory concentration greater than or equal to six mg/ml, primarily compounds containing a nor-chenodeoxycholane moiety with IC_{50} values similar to natural alkaloids used for treatment, and selectivity averages within the scope of 5.6–15.7 (Leverrier et al., 2013).

76.3.3 ANTIARRHYTHMIC EFFECT

Quinidine was the most commonly prescribed medicine for the treatment of cardiac arrhythmias. Quinidine was the most effective antiarrhythmic chemical extracted from the *Cinchona pubescens* in studies conducted in the mid-20th century. Quinidine was used as an antiarrhythmic medication since the 1920s to maintain sinus rhythm following a transition from atrial flutter or arrhythmia and to prevent ventricular tachycardia or ventricular fibrillation. Its efficacy in the long-term in prevention of ventricular arrhythmia relapses was questioned after a meta-analysis and it revealed that quinidine use increases mortality. Due to much evidence of increased risk for the appearance of ventricular arrhythmia, unexpected death, and other harmful effects, quinidine was withdrawn from usage and has since been unavailable in many countries. On the other hand, ongoing research has revealed that quinidine is orally prescribed that has consistently demonstrated practicality in preventing arrhythmias and ceasing perturbations caused by repetitive ventricular fibrillation in patients with Brugada disorder, idiopathic ventricular fibrillation, and early repolarization condition. Quinidine is the only antiarrhythmic medicine that has been shown to standardize the QT interval in people with congenital short QT syndrome (Bozic et al., 2018). Quinidine and quinine show additional anticholinergic properties resulting in a consistent rate of improvement of the heartbeat. Antiarrhythmic has been appropriated already in BrS-related electrical perturbations of heart. A dual drug mixture of orciprenaline and quinine was used to terminate the electrical perturbation in a study. Instead of quinidine, quinine was used initially as an off-mark drug while not being approved as antiarrhythmic to treat presumably severe electrical perturbations since antiarrhythmic was not quickly accessible when AstraZeneca halted its production in 2006. It has to be underscored that orciprenaline and quinidine were used as a sensible approach in an electrical perturbation which restricts repeated BrS, whereas in most electrical perturbations correlated with ischemic or enlarged cardiomyopathy, orciprenaline or quinidine application may cause life-threatening consequences. For adequate long-run treatment of arrhythmias, orciprenaline was suspended, and quinine was replaced by quinidine (Schweizer et al., 2010).

Quinidine is a quinine stereoisomer that is used as a type of IA antiarrhythmic medication. Quinine and quinidine have similar effects and have been used interchangeably in the past. Quinine and quinidine both check the cardiac activity potentially by inhibiting the internal sodium current (INa), promoting posterior depolarization, and lengthening the QRS complex; they

are inotropic, like other class 1 antiarrhythmic medicines (Phillips et al., 2012). Quinidine has two significant electrophysiologic effects: prolonging of recalcitrance and the conduction time. Electrophysiologic effects of quinidine and its stereoisomer quinine (which was used to induce conduction time but not recalcitrance) in animal models with supported ventricular tachyarrhythmia late after ischemic injury, which were studied to see which of these influences antiarrhythmic effect. Quinidine (3 of 12) had antiarrhythmic viability; while neither of quinine (0 of 15) had the effect (Sheldon et al., 1990).

76.3.4 ANTI-DIABETIC ACTIVITY

A study was conducted to know the antidiabetic effects of bark hydro-extract of *Cinchona calisaya* on diabetic Wistar rats (alloxan-provoked diabetes; i.p injection of 150.0 mg/kg bw. of alloxan monohydrate, intraperitoneally). *C. calisaya* bark hydro-extract; injected intraperitoneally to the treatment groups (50.0 and 100.0 mg/kg BW). Glibenclamide (0.3 mg/kg body. wt.) was used as a standard. *C. calisaya* bark extract produced a 64.4% decrease in blood glucose content following four days of periodic injection. The extract produced a notable reduction in the blood glucose content in the treatment groups for both doses. The outcomes on the antioxidant activity indicated that *C. calisaya* extracts improved the lipid peroxidation (LPO) and SOD activity related to control. Phytochemical examination revealed the presence of flavonoids (5.0%), saponins (2.0%), cardiac glycosides (3.54%) and alkaloids (6.0%) (Ezekwesili et al., 2012). Many plants with hypoglycemic activity have already been postulated to act on blood glucose by inhibiting endogenous glucose synthesis or inhibiting gastrointestinal glucose absorption (Musabayane et al., 2006). Outcomes of the qualitative phytochemical experiments showed that the *C. calisaya* extract has measurable amounts of alkaloids, flavonoids, saponins, cardiac glycosides, and carbohydrates with lesser content of tannins. At least one of these phytochemicals could be a reason for the extracts' marked antidiabetic and antioxidant activities (Edeoga et al., 2005).

76.3.5 ANTIMALARIAL EFFECT

Quinine, an alkaloid extracted from the Cinchona tree, was the most effective antimalarial medication. Quinine, quinidine, cinchonine, and cinchonidine are all alkaloids found in the *Cinchona* genus. For nearly 400 years,

Cinchona bark has been used as an antimalarial treatment (Gisselmann et al., 2018). Chloroquine was developed as a synthetic substitute for quinine in the early 1900s. It was the medicine of choice for malaria treatment for a long time since it was potent, modest, and less toxic. Due to parasite resistance to quinine, its usage has been limited in malarial treatment. Mefloquine is most commonly associated with quinine and has been used to treat intestinal ailments, but its usage is restricted due to interference with neuropsychiatric effects (Uzor, 2020). Quinine is immediately given orally or through intravenous, intramuscular, or subcutaneous injection, reaching peak activity within one to three hours. It is disseminated throughout the whole-body fluids and is particularly enzyme mediated. The degree of dissemination in individuals with severe malaria is lesser than the healthier people, and it depends on the severity of the infection. People with the intestinal illness have greater bloodstream quinine levels. Because of an increased concentration of alpha-1 acidic glycoprotein in malaria patients, protein binding of quinine is increased (Achan et al., 2011). The use of quinine has been linked to severe hypoglycemic condition, but the effects of quinidine and other antimalarial drugs on glucose homoeostasis have not been investigated (Phillips et al., 1986).

Quinine from *C. calisaya* acts against the four species of human malaria parasites' asexual erythrocytic forms (Eyal, 2018). Quinine is ineffective against parasites at the liver infection stage (Vinetz et al., 2017). Ronald Ross identified *Anopheles* mosquitos as the malaria vector after finding "a few granules of black pigment completely similar in appearance with the well-known and distinctive pigment of the malarial parasite" in the stomach wall of *Anopheles* mosquito (Martin, 1999). This pigment was discovered to be hemozoin, an insoluble crystalline substance that was suppressed by quinoline-containing drugs by inhibiting a heme-polymerase enzyme (Slater and Cerami, 1992). Nearly 120 years after Ross's discovery, Olafson et al. (2017) demonstrated that the adsorption of quinine and other quinolone drugs to the crystal surfaces is the primary mechanism of crystal growth inhibition,

76.3.6 ANTI-VIRAL EFFECT

An investigation was done on the target protease in the novel coronavirus for COVID-19 therapy. The 6LU7 is the primary protease located in the COVID-19 (Li, 2020). A molecular-docking procedure (automated, *in silico*) was performed using the SwissDock server based on the docking algorithm EADock ESS to identify the potential binding positions for antimalarial compounds (Grosdidier et al., 2011). Familiar antimalarial compounds

chloroquine ($C_{18}H_{26}ClN_3$), quinine ($C_{20}H_{24}N_2O_2$) and hydroxychloroquine ($C_{18}H_{26}ClN_3O$) were used as a ligand to the COVID-19 protease. Log P and log S values were computed to estimate their biological action. Log S is an essential factor influencing the bioavailability of drugs, and log P is linked to the movement characteristic of drugs and their interplay with receptors. The log P and S values of hydroxychloroquine are 3.87 and –4.11; Chloroquine has a log P and S values of 5.28 and –4.26; Quinine has a log P and S values of 2.82 and –2.99, respectively. In common, nearly 85% of drugs have log S values ranging from –1 to –5 (Jorgensen and Duffy, 2000). These log S and log P values imply that the molecules might have quick dispersal through the cell membranes, and their organic solubility is considerably high. The results predicted that hydroxychloroquine and chloroquine could be the potential compounds to inhibit COVID-19.

The docking parameters such as the FF score, amino acid residues located in the active site pockets of 6LU7, and the binding energy were recorded. The binding affinities acquired through 6LU7 docking by ligands hydroxychloroquine and quinine has H-bonds with histidine (HSD-163), a polar amino acid with a bond length of 2.377 Å and phenylalanine (PHE-140), an aromatic amino acid with a bond length of 2.501 Å, whereas chloroquine forms H-bond with a bond length of 2.321 Å with the glycine (GLY143), a non-polar amino acid. The binding affinities acquired from docking of 6LU7 with ligands chloroquine, quinine, and hydroxychloroquine were –8.15, –7.77, and –7.62, kcal/mol, sequentially. The docking investigations imply that antimalarial drug compounds can repress COVID-19 protease (6LU7) (Srivastava et al., 2020).

Smear analysis of SARS-CoV-2 infected Vero B4 cells revealed that quinine had antiviral activity against SARS-CoV-2 virus. By examining the fluorescence endpoint and time-lapse in SARS-CoV-2-m Neon Green-fluorescent Caco-2 cells, researchers confirmed that quinine has a similar antiviral effect in a human-derived cell line. It was found that quinine could be a viable and widely used therapeutic option for SARS-CoV-2 infections (Große et al., 2020). Dengue infection (DENV) outbreaks continue to spread worldwide, resulting in high mortality and financial losses. Even though no medicine has been approved to combat the infection, quinine reduces DENV infection by 80% compared to other drugs. Additionally, quinine restrained DENV infection in four different serotypes of DENV. Quinine effectively halted DENV replication by reducing the viral protein load and hence, dengue infection. These findings support the use of quinine to boost antiviral properties; it can reduce dengue infection and slows down replication of the

virus. The antiviral activity of quinine discovered could be helpful in the development of novel DENV drugs (Malakar et al., 2018).

76.3.7 ANTIBACTERIAL EFFECT

The antibacterial property of quinine dihydrochloride against various gram-positive and negative pathogenic microbes was investigated systematically. *Streptococcus pyogenes, Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli*, and S*almonella typhi* were examined by exposing it to quinine dihydrochloride. Quinine dihydrochloride had a bactericidal effect against all the microbes (Wolf et al., 2002). Rennie et al. (2003) observed that quinine sulfate inhibited the growth of *Enterobacter agglomerans, Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiella pneumoniae*. Quinine sulfate inhibited *Escherichia coli* infection; Quinine dihydrochloride may reduce the need for additional antibacterial drugs for patients under malarial treatment (Kharal et al., 2009). The co-inoculation of sterilized *Aspergillus niger* mycelia and the parasite *Phytophtora cinnamomi* to *Cinchona ledgeriana* suspension cultures resulted in increased concentration of anthraquinone. This discovery, combined with the antibacterial activity of anthraquinones isolated from *Cinchona pubescens* callus cultures, concluded that anthraquinones are phytoalexins (Wijnsma et al., 1985).

An experiment was conducted to examine the antibacterial action of *Cinchona calisaya* (bark extract) against *Staphylococcus aureus* using the agar disc dispersion technique. The plates were inoculated with *S. aureus* and incubated at 37°C for 24 hours. Various concentrations *viz*, 25, 50, 75, and 100 µl of bark ethanolic extract (EE) *of C. calisaya* revealed the zone of inhibition of *Staphylococcus aureus* showing 4, 6, 9, and 17 mm. The zone of inhibition area increased with a dose-dependent mode. The study concluded that *Cinchona calisaya* could be a possible source to explore for naturally occurring antimicrobial drugs (Kushwah et al., 2016).

76.3.8 ANTICANCER EFFECT

In a study, K562/ADM (human leukemic cell line, multidrug-resistant) was used to examine the influence of cinchonine and quinine on vincristine, mitoxantrone, and doxorubicin uptake and cell death in *in-vitro* conditions. Quinine at 40 microM concentration provoked a concentration-dependent rise in doxorubicin uptake, spanning about 200%. Quinine had a very sparse (mitoxantrone) and nil (vincristine) impact on uptake. Besides,

cinchonine caused an accelerated and notable improvement in the uptake of all compounds (vincristine, mitoxantrone, and doxorubicin), attaining stability at 5 and 10 micro-molar concentration. Cinchonine and quinine in combination provoked potent cytotoxicity effects in K562/ADM cells along with mitoxantrone, vincristine, and doxorubicin; nevertheless, quinine at 10 microM attained a plateau phase. Cinchonine at low concentrations (five microM) had a significantly potent effect on K562/ADM cells. When blended in blood plasma, quinine was more bound to proteins than cinchonine. Plasma proteins slightly modified Cinchonine-provoked cellular uptake and accumulation of vincristine. Incubation of cinchonine in whole blood, a fraction of cinchonine confined in RBCs, was swiftly exchangeable with blood plasma. The study concludes that cinchonine can potentially repress MDR compared to quinine (Genne et al., 1992). Spectrophotometric methods were used to determine the antioxidant activity of *C. pubescens* extracts through DPPH and ABTS methods. The IC_{50} value for DPPH (42.00 ± 0.2 ug/ml) and ABTS (88.00 ± 0.2 IC_{50} ug/ml) (Noriega et al., 2015).

A study was conducted to examine the apoptosis effect of quinine against laryngeal cancer cell lines (HEp-2). MTT assay was conducted to measure cytotoxicity. Morphological changes of the cancer cells, mitochondrial membrane potential, apoptosis levels of ROS, and flow cytometry were done. In the MTT assay, the mean inhibition concentration (IC_{50}) of quinine was found to be 123.74 μM/ml for 48 hours and 147.58 μm/ml for 24 hours. The series of events has shown modulation of reactive oxygen species (ROS), progression of apoptosis by the decline of cell viability, and cell cycle check within the G0/G1 phase induction on HEp-2 cells. The results concluded that quinine has a cytotoxic impact on carcinoma cells, and it might be considered a novel compound for tumor control (Krishnaveni and Suresh, 2015).

Quinidine and its derivates were accounted to have properties of improving the movement of anticancer medications by suppressing the activities of P-glycoprotein (P-gp) and cytochrome P450 (Xing et al., 2013). Like an anticancer drug, Quinidine can trap MCF-7 cells responsible for breast cancer tumors in the G1 phase of the cell cycle, resulting in the death of cancerous cells (Wang, 1998). Quinine and cinchonine from *C. calisaya* have been studied in the reversal of multidrug resistance (MDR) in cancer patients for the past two decades. Clinical trials for quinine at stage I/II shows that it can be safely combined with anticancer agents such as paclitaxel, mitoxantrone, cyclophosphamide, cytarabine or in the treatment of clinically resistant acute non-Hodgkin's lymphomas, breast cancer or leukemias (Warhurst et al., 2003). Unfortunately, there was only a moderate achievement in patients

with acute Phase III leukemia in preliminary studies (Solary et al., 2003). MDR reversal activity was seen in cinchonine, and it could be securely administrated to patients with malignant lymphoid disease where cinchonine can be combined with methylprednisolone, cyclophosphamide, vinblastine, and doxorubicin (Solary et al., 2000). In an *in vitro* study with MCF-7/DX1 cells, dimeric quinine 85 was highly active in completely reversing the P-gp-mediated paclitaxel resistance phenotype and restricting its transport (Pires et al., 2009). Inhibitory activity of quinine for microbial pathogen infection on human skin was observed. Quina bark treats lumbago, heart problems, cancer, colds, amoebic infections, and diarrhea (Kacprzak, 2013).

76.3.9 EFFECTS ON HUMAN MUSCLE NICOTINIC ACETYLCHOLINE RECEPTORS

Cinchonidine, quinine, cinchonine, quinidine are the alkaloids found in *Cinchona* sps. For nearly 400 years, Cinchona bark has been used as an antimalarial treatment. Quinine was initially isolated in 1820 and is still used to treat malarial fever caused by *Plasmodium falciparum*; it has also been used to treat leg cramps in lesser doses. The derivatives of quinolone *viz,* quinine, chloroquine, and quinidine revealed synapses effects in the brain of the adult and the embryonic muscles of *Xenopus laevis* oocytes. The mixture of compounds inhibited acetylcholine (ACh)-provoked reactions in *Xenopus laevis* oocytes with a concentration of chloroquine (IC_{50} = 2.22 M), quinidine (IC_{50} = 3.96 M, and quinine (IC_{50} = 1.70 M). The activities of the quinine molecules were independent of ACh concentration. In conclusion, quinine has been postulated as a repressor of ACh-induced reactions (Gisselmann et al., 2018).

KEYWORDS

- ***Cinchona pubescens***
- ***Cinchona calisaya***
- **quinine**
- **antimalarial**
- **reactive oxygen species**
- **toll-like-receptor-2**

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CHAPTER 77

Phytochemical Constituents and Pharmacology of *Areca catechu* L.

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77.1 INTRODUCTION

Areca catechu L. (Syn.: *Areca cathechu* Burm.f., *Areca faufel* Gaertn., *Areca himalayana* Griff. ex H.Wendl., *Areca hortensis* Lour., *Areca macrocarpa* Becc., *Areca nigra* Giseke ex H.Wendl., *Sublimia areca* Comm. ex Mart.)

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belongs to the family Arecaceae. Vernacular names of this plant include udveg, pugaphal, pugi, akoth, chamarpushpa, pugh, valktaruh, guvakah, khapur (Sanskrit), chamarpushpa, supari, pungi, guvak, khapur, guwa, pugi, pug (Hindi), chempalukka, adakka, kazhangu, kavung, kavungu, adakkamaram, kamuk, pakku (Malayalam), ataikkay, pukam, kamuku, vimpu, chamara-putpam, kuntar-kamaku, chakuntam, kanti (Tamil), adake, adike (Kannada), pophala, supari (Konkani), ghonta, pugamu, kramukamu, poka, khapuramu (Telugu), pugaphal, supari, pophal pophali, pugiphala, pug (Marathi), sopari, ayrike (Gujarati), supari (Bengali), tamol-goch (Assamese), kwa pambi (Manipuri), pinang (Bahasa Indonesia), jambe (Javanese), pinang (Malay), bunga, takotob, boa (Filipino), mak (Thai), cau, binh lang, tân lang (Vietnamese), betel nut, palm, areca nut, pinang, areca palm, betel nut palm (English).

Stems erect, hooped, unarmed. Leaves in a terminal crown, to 2 m long; leaflets many, linear or linear-lanceolate, base narrow, apex praemorse; lower ones plicate; upper ones coherent. Spadices several on the axils of fallen leaves, to 50 cm long, branched, shortly peduncled; spikes flexuous or straight, to 30 cm long. Flowers monoecious; lower one's female, 1–3 at spike-base; upper one's male, many. Fruit to 4 × 2.5 cm, with fibrous mesocarps, orange-red in color (Sasidharan, 2004). It is native to the Philippines and is widely distributed in southern and Southeast Asia, including India, China, Indonesia, Malaysia, New Guinea, etc.

In Chinese Pharmacopoeia, over 100 drug preparations are used to treat parasitic diseases, dyspepsia, abdominal distension, abdominal pain, diarrhea, edema, jaundice, etc., containing areca nut as an ingredient. In Chinese *Mingyi Bielu* (TCM monograph), areca nut was described for its diuretic, digestion-promoting, and anti-parasitic properties. In *Xinxiu Bencao* (TCM monograph), the areca nut was described as a treatment for abdominal distension, and in *Compendium of Materia Medica* (*Bencao Gangmu*), its name mentioned for the treatment of dysentery, abdominal distension, and constipation. The Indian systems of medicine also use areca nut as a popular digestive, astringent, and emmenagogue. In Cambodia, areca nut is used to treat diarrhea, dysentery, and liver disorders. In Malaya, areca nut is used to treat lumbago and abdominal distension (Caius, 1934; Raghavan and Baruah, 1958; Amudhan et al., 2012). In addition to its medicinal application, areca nut is also used as a daily food ingredient in Chinese Taipei, and South and Southeast Asia and is considered as the fourth most used addictive stimulant, after caffeine, nicotine, and alcohol (Heatubun et al., 2012). The immature fruit or pericarp of *A. catechu* is the main constituent of betel quid, and

chewing betel quid is strongly associated with the archaic oriental culture (Lim and Kim, 2006; Benegal et al., 2008).

77.2 PHYTOCHEMICAL CONSTITUENTS

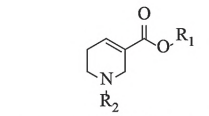
Pyridine-type alkaloids and tannin derivatives have been identified as the characteristic secondary metabolites of *A. catechu* (Peng et al., 2015). *A. catechu* is the only plant containing alkaloids of the Arecaceae family and the total alkaloid content is approximately 0.3–0.7% (Zeng et al., 2006; Xu, 2001). Huang and co-workers isolated arecoline (0.3–0.6%), the major alkaloid of *A. catechu* (Huang and Michael, 1989). The predominant alkaloids of the pyridine type are asarecoline and its derivatives arecaidine, guavacoline, guavacine, arecolidine, methyl nicotinate, ethyl nicotinate and nicotine (Jahns, 1888; Raghavan and Baruah, 1958; Holdsworth et al., 1998).

Zhang et al. (2009) first reported the isolation of flavonoids from *A. catechu*, includes isorhamnetin, luteolin, quercetin, chrysoeriol, liquiritigenin, and jacareubin. Proanthocyanidins, also called condensed tannins are another characteristic component of *A. catechu*. The major classes of tannins in *A. catechu* are the catechuins and its enantiomer epicatechuins. The specific tannin compounds of *A. catechu* include dimeric catechuins such as procyanidin A1, procyanidin B1 and its enatiomer procyanidin B2. A trimeric, tetrameric, and pentameric form of catechuins also reported from *A. catechu* such as arecatannin A1, arecatannin B1, arecatannin B2, arecatannin C1, arecatannin A2 and arecatannin A3 (Nonaka et al., 1981; Ma et al., 1996; Yang et al., 2012).

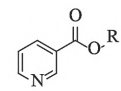
Saeed et al. (1993) reported the pentacyclic triterpene, ursolic acid and its derivative 3-acetyl ursolic acid from the leaves of *A. catechu*. Arborinol, arborinol methyl ether, fernenol, and arundoin were isolated from the pericarp of *A. catechu* (He et al., 2010; Yenjit et al., 2010). A triterpene named cycloartenol and three tetracyclic steroids, β-sitosterol and its derivatives 5,8-epidioxiergosta-6, 22-dien-3-ol and stigmasta-4-en-3-one were isolated from the seeds of *A. catechu* (Yang et al., 2012).

The major fatty acids in *A. catechu* are lauric acid, myristic acid, palmitic acid, stearic acid, and oleic acid (Kiuchi et al., 1987). He et al. (2010) reported two emodin-type anthraquinones, chrysophanol, and physcion from the pericarp of *A. catechu*. Zhang et al. (2010) isolated p-hydroxybenzoic acid, epoxyconiferyl alcohol, 4-[3′-(hydroxymethyl) oxiran-2′-yl]-2,6-dimethoxyphenol, protocatechuic acid and isovanillic acid from the seeds of

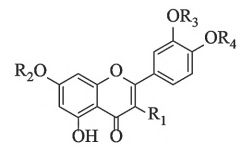
A. catechu. Yang et al. (2012) reported resveratrol, ferulic acid, vanillic acid and de-O-methyllasiodiplodin from the seeds of *A. catechu*.



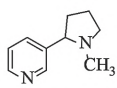
Arecoline; R_1 =CH, R_2 =CH$_3$
Arecaidine; R_1 =H, R_2 =CH$_3$
Guavacoline; R_1 =CH$_3$, R_2 =H
Guavacine; R_1 =H, R_2 =H
Arecolidine; R_1 =OEt, R_2 =CH$_3$



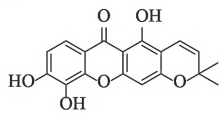
Methyl nicotinate; R=CH_3
Ethyl nicotinate; R=Et



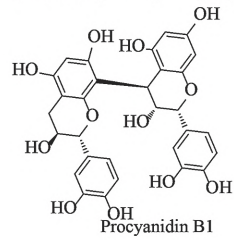
Isorhamnetin; R_1 = OH, R_2 = CH_3, R_3 = H
Luteolin ; R_1 = H, R_2 = H, R_3 = H
Quercetin; R_1 = OH, R_2 = H, R_3 = H
Chrysoeriol; R_1 = H, R_2 = CH_3, R_3 = H



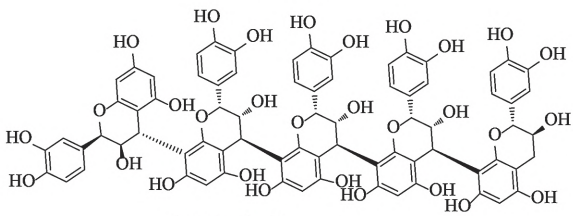
Nicotine



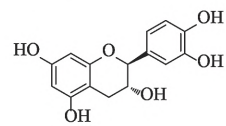
Jacareubin



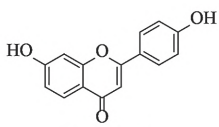
Procyanidin B1



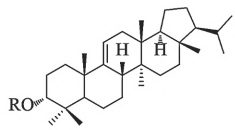
Arecatannin A3



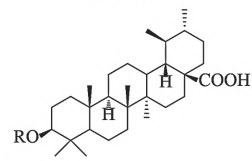
Catechuins



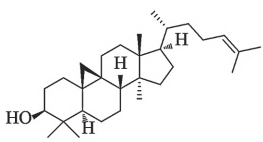
Liquiritigenin



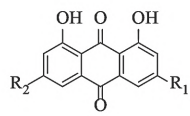
Arborinol; R= H
Arborinol methyl ether R=CH_3



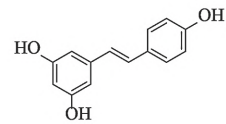
Ursolic acid; R= H
3-Acetyl ursolic acid R=Acetyl



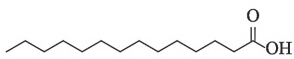
Cycloartenol



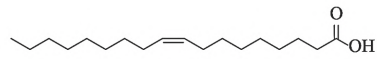
Chrysophanol; R_1 =CH$_3$, R_2 =H
Physcion; R_1 =OCH$_3$ R_2 =CH$_3$



Resveratrol



Oleic acid



Myristic acid

77.3 PHARMACOLOGICAL STUDIES

Extracts and isolated compounds of various parts of the *A. catechu* showed a wide range of pharmacological properties and are discussed in subsections.

77.3.1 GASTROPROTECTIVE ACTIVITY

Gastrointestinal motility in rabbits (0.05, 0.25, and 0.5 μg/ml) and in mice (2.5 and 5 mg/kg) were significantly increased with the treatment of water extract of areca nut, via stimulation of the M receptor and verapamil sensitive Ca^{2+} channel (Yang et al., 2002; Li et al., 2011a). Zou et al. (2003a, b, 2007) reported that the water extract of areca nut significantly improved the gastrointestinal function of rats with functional dyspepsia. Studies reported that the water extract of areca nut (0.25 and 1 g/ml) markedly enhanced the gastrointestinal motility in rats, via increasing substance P and motilin, and decreasing vasoactive intestinal peptide (Guo, 2008; Guo et al., 2008). Xie et al. (2002) reported that water extract of areca nut (10, 100, and 1,000 mg/ml) dose-dependently increased the contraction of the colonic muscle strips of rats through a mechanism possibly associated with the stimulation of the M receptors. Ethyl acetate (EAE) extract of the areca nut (10, 30, and 50 mg/kg) significantly affect the gastrointestinal motility in mice (Yuan et al., 2009). Li et al. (2013) found that fraction separated from the water extract of areca nut (0.01, 0.1, 1, and 10 mg/ml) significantly promotes gastric smooth muscle contraction in rats. Ni et al. (2004) reported that arecoline (0.06%) containing water extract of areca nut significantly increases the contraction of gastric smooth muscle and muscle strips of the duodenum, ileum, and colon.

77.3.2 ANTIOXIDANT ACTIVITY

Ahn et al. (2009) demonstrated that ethanol extract of areca nut has a potent DPPH radical scavenging activity (EC_{50} 4.5 μg/ml). In another study by Khan et al. (2011) showed that ME of areca nut and its water fraction possess good DPPH radical scavenging activity (IC_{50} 5.34 μg/ml and 7.28 μg/ml). The water extract of areca nut showed significant radical scavenging activity against DPPH (EC_{50} 1.38 μg/ml) and hydroxyl radicals (EC_{50} 1,150 μg/ml); and also showed iron (II)-chelating (EC_{50} 2966.87 μg/ml) and lipoxygenase (LOX) inhibitory (EC_{50} 25.7 μg/ml) activities (Pithayanukul

et al., 2009). Bhandare et al. (2010) demonstrated that ethanol extract of areca nut showed hydroxyl radical-scavenging activity (IC_{50} 83.14 μg/ml). Zhang et al. (2010) isolated some compounds from areca nut, showed good DPPH radical scavenging activity; 4-[3′-(hydroxymethyl)oxiran-2′-yl]-2,6-dimethoxyphenol (EC_{50} 41.8 μM), epoxyconiferyl alcohol (EC_{50} 81.7 μM), isovanillic acid (EC_{50} 124.9 μM), protocatechuic acid (EC_{50} 73.4 μM), p-hydroxybenzoic acid (EC_{50} 182.4 μM), isorhamnetin (EC_{50} 146.6 μM), chrysoeriol (EC_{50} 172.2 μM), luteolin (EC_{50} 32.8 μM), (±)-4′,5-dihydroxy-3′,5′,7-trimethoxyflavonone (EC_{50} 255.7 μM), (2S,3R)-ent-catechuin (EC_{50} 19.2 μM) and jacareubin (EC_{50} 19.7 μM). Hamsar et al. (2011) demonstrated that the methanol and water extracts (WEs) of the ripe nut, unripe nut, roots, and adventitious roots of *A. catechu* showed good DPPH radical scavenging activity with EC_{50} values 0.021, 1.87, 2.83, 2.71, 2.49 μg/ml, and 2.04, 3.35, 3.35, 2.69, 2.58, μg/ml, respectively. Ethanol extract of areca nut (500, 1,000, 2,000 mg/kg/day, p.o., for 28 days) showed protective effect in carbon tetrachloride induced liver injury in rats by decreasing the levels of serum aspartate aminotransferase (AST), AST and malondialdehyde (MDA) (Pithayanukul et al., 2009).

77.3.3 ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES

Procyanidin rich acetone extract of areca nut (0.1–1 μg/ml) significantly down regulated the expression of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced cyclooxygenase-2 by inhibiting extracellular-signal-regulated kinase (ERK) phosphorylation in SAS cells. Further, 5 days treatment with acetone extract (1 and 10 mg/kg/day) suppressed the carrageenan-induced inflammatory edema and prostaglandin E2 (PGE2) levels in rats (Huang et al., 2010). Bhandare et al. (2010) found that ethanol extract of areca nut (250, 500, and 1,000 mg/kg) showed significant dose-dependent analgesic and anti-inflammatory activities in different animal models. Ethanol extract of areca nut was found to be effective against nitroglycerin induced delayed inflammatory migraines in rats. In addition, the extract at doses of 250 and 500 mg/kg suppressed the plasma protein extravasation in models of both intravenous and topical nitroglycerin application via inhibition of inducible nitric oxide (NO) synthase (iNOS) (Bhandare et al., 2011). Khan et al. (2011) reported that ME of areca nut and its water fraction (100 mg/kg) showed significant anti-inflammatory and analgesic effects in mice and rats' models via suppression of the expression of PGE2 and arachidonic acid.

Saeed et al. (1993) found that ursolic acid (25, 50, and 100 mg/kg) isolated from the leaves of *A. catechu* showed significant anti-inflammatory effect in carrageenan-induced paw edema in mice.

77.3.4 ANTI-ALLERGIC ACTIVITY

Water extract of the areca nut inhibited the dinitrophenyl-*bovine serum albumin* and compound 48/80 induced degranulation in RBL-2H3 mast cells (IC_{50} 53 and 52 mg/mL, respectively) and at a dose of 300 mg/kg water extract of the areca nut significantly inhibited the compound 48/80 induced systemic anaphylaxis in mice (Lee et al., 2004). Hung et al. (2006) found that the water extract of ripe areca nut without husk (25, 50, 75, and 100 μg/ml) and tender areca nut with husk (200, 400, 600, and 800 μg/ml) of *A. catechu* significantly inhibited the phagocytic activity of neutrophils in a concentration dependent manner. Lai et al. (2007) found that water extract of areca nut (25 and 50 mg/ml) reduces the release of myeloperoxidase (MPO) from human polymorphonuclear leukocytes. In splenocytes stimulated with the phorbol-12-myristate-13-acetate plus ionomycin, water extract of areca nut suppressed the release of interleukin-2 (IC_{50} 42.8 μg/ml) and interferon-γ (IC_{50} 38.1 μg/ml) (Wang et al., 2007).

77.3.5 CARDIOPROTECTIVE ACTIVITY

In male spontaneous hypertensive rats and age-matched Wistar-Kyoto normotensive rats, the tannin rich fraction of areca nut extract (100 and 200 mg/kg) possess potent antihypertensive action via inhibition of angiotensin converting enzyme (Inokuchi et al., 1986). Arecoline rich fraction of areca nut WEs relaxed aortic ring preparations of isolated rat aorta that contained endothelium from 3×10^{-7} g/ml, reaching a maximum of 86% at 10^{-5} g/ml (Goto et al., 1997). Ghayur et al. (2011) demonstrated that the ME of areca nut significantly inhibited the platelet aggregation induced by arachidonic acid, adenosine diphosphate, platelet-activating factor (PAF), epinephrine, or Ca^{2+} ionophore, with IC_{50} values of 1.59, 0.628, 1.902, 1.677, and 0.987 mg/ml, respectively. Catechin isolated from areca nut inhibited the platelet aggregation induced by arachidonic acid, adenosine diphosphate, PAF, epinephrine, or Ca^{2+} ionophore, with IC_{50} values of 3.630, 1.876, 2.551, 1.541, and 2.640 mg/ml (Ghayur et al., 2011).

77.3.6 ANTIHYPERLIPIDEMIC ACTIVITY

Rats fed with high fat diet (HFD) containing free cholesterol (1%, w/w) and ethanol extract of areca nut (0.5% w/w), for one week significantly decreased the plasma cholesterol level (25%). It also significantly decreased the small intestinal pancreatic cholesterol esterase and acyl-CoA cholesterol acyltransferase activities (Park et al., 2002). Rat supplemented with water extract of areca nut (0.5%, w/w) significantly decreased the absorption of triglycerides and plasma lipids (Byun et al., 2001; Jeon et al., 2000). The ME of areca nut (10, 30, and 50 mg/kg) significantly decreased the serum levels of total cholesterol (TC) and triglycerides, as well as the atherogenic index (Yuan et al., 2009).

77.3.7 ANTIDIABETIC ACTIVITY

Procyanidin rich acetone extract of the areca nut (1 and 10 μg/ml) significantly, inhibits the cyclic adenosine monophosphate/dexamethasone induced gluconeogenesis in mouse primary hepatocytes. In streptozocin-induced hyperglycemic mice, the procyanidin rich acetone extract (10 mg/kg, p.o. for 4 weeks) significantly decreased the fasting blood glucose. Furthermore, there was a tendency toward restoration of the level of 5′-AMP-activated protein kinase (AMPK) expression (Huang et al., 2013). In alloxan-induced diabetic rats, the phenolic rich ethanol and aqueous extracts of the flowers of *A. catechu* (500 mg/kg, p.o. for 21 days) showed potent antidiabetic activity (Ghate et al., 2014).

77.3.8 NEUROPROTECTIVE ACTIVITY

Hexane (2.5, 5, 10, and 13 mg/kg) and water (2.5, 5, 10, 13, 20, and 50 mg/kg) extracts of areca nut showed significant dose dependent anti-depressive effects in mice and rats. The extracts significantly decreased the levels of monoamine oxidase in rat brain homogenates (Dar et al., 1997). Dar and Khatoon (2000) found that dichloromethane (DCM) extract (1, 4, 7, 10, and 13 mg/kg) of areca nut showed anti-depressive effect by decreasing the levels of monoamine oxidase in mice and rats. Khan et al. (2014) found that DCM extract (7 mg/kg) regulates the levels of monoamines, including serotonin and dopamine. Phenolic acid rich pericarp extract of *A. catechu* (80, 160, and 320 mg/kg) showed significant anti-depressant activity in mice

(He et al., 2012). Abbas et al. (2013) found that ethanol extract of areca nut and its sub-fractions possess significant anti-depressant activities in both the acute and sub-chronic forced swim tests (IC_{50} 20–50 mg/kg). Arecaidine and guvacine isolated from the *A. catechu* are effective antagonists of gamma-aminobutyric acid, with IC_{50} values 122 μM and 8 μM, respectively (Johnston et al., 1975; Lodge et al., 1977). ME of areca nut (1–100 μg/ml) showed inhibitory action on acetylcholinesterase (AChE) *in vitro* (Gilani et al., 2004). Arecoline (0.1–1.0 mM) inhibits the release of the peripheral catecholamines via activation of cholinergic receptors (Lim and Kim, 2006). DCM extract (125 and 175 mg/kg) of the areca nut suppressed the withdrawal symptoms in morphine-dependent mice (Kumarnsit et al., 2005). Arecoline (0.25, 0.5, and 1 mg/kg, i.p.) significantly increased sobriety and improved hangover symptoms in ethanol exposed mice (Sun et al., 2005). ME of areca nut (10, 30, and 50 mg/kg) showed dose dependent anti-fatigue effect in mice by increasing the liver glycogen and decreasing serum levels of nitrogen and lactic acid (He et al., 2009).

77.3.9 ANTIMICROBIAL ACTIVITY

Pre-treatment with ME of areca nut (50 mg/kg, 7 days) significantly improved the survival rate of mice inoculated with *Staphylococcus aureus* when compared to control group (70% vs. 10%) (Li et al., 2007). Boniface et al. (2014) found that ME and its sub-fractions (including ethylacetate, butanol, and water fractions) possess good antibacterial activity against *S. aureus*, with minimal inhibitory concentration values of 125, 250, 62.5, and 250 μg/ml, respectively. Arecoline showed good antibacterial activity against *Bacillus proteus*, *Candida albicans* and *Bacillus anthracis*, with MIC value 0.8 mg/m each (Luo et al., 2010). Fernenol, arundoin, a mixture of stigmasterol and β-sitosterol, and lauric acid isolated from the pericarps of *A. catechu* showed notable antifungal effects against *Colletotrichum gloeosporioides*, with MIC values 36.7, 47.5, 56.7, and 111.5 μg/ml, respectively (Yenjit et al., 2010).

77.3.10 ANTIPARASITIC ACTIVITY

Arecoline isolated from the water extract of areca nut was found to be effective against tapeworms by paralytic effect (Zheng, 1999). Zha et al. (1990) reported that decoction of the areca nut (1%) effectively kills blood

flukes by disrupting their nervous systems. Arecoline showed significant synergetic effect with pentachlorophenol sodium and esculentoside against *Oncomelania*, by regulating smooth muscle contractions of the feet (Feng et al., 1999; Li et al., 2000; Yao et al., 2001). Boniface et al. (2014) found that butanol fraction of the ME of areca nut showed good activity against *Plasmodium falciparum* (IC_{50} 18 μg/ml).

77.3.11 TOXICITY STUDIES

Chiang et al. (2004) found that long-term habit of chewing areca nut can cause weight loss and decrease of survival rates in hamsters. Water extract of areca nut (200 μg/ml) and arecoline (10 μg/ml) significantly up-regulated the mRNA expression of the c-jun protooncogene, an indication of oral squamous cell carcinoma (Jeng et al., 1994; Ho et al., 2000). Studies reported that the water extract of areca nut (40–80 μg/ml) causes a significant proliferative effect on oral mucosal fibroblasts via up-regulation of the expression of intercellular adhesion molecule-1 (Feng and Ling, 2003; Li and Ling, 2006). Li et al. (2011b) reported that arecoline (100 and 125 μg/ml) induced apoptosis in HaCaT cells. Oligomeric procyanidin rich areca nut extract (20–1,000 μg/ml) markedly induced splenic lymphocyte apoptosis (Wang et al., 2009). In albino mice, arecoline at a dose of 5 mg/kg, i.p., for 14 days reported splenic lymphocyte cell cycle arrest and induced apoptosis at higher doses (10–20 mg/kg, i.p., for 14 days) (Dasgupta et al., 2006). Chou et al. (2008) found that arecoline (0.1–1 mM) showed cytotoxic effect in normal hepatocytes (clone-9 cells), by inducing apoptosis and G0/G1 cell cycle arrest. Water extract of areca nut showed a decrease in sperm counts, motility, and abnormalities in sperm morphology (Hu et al., 1999; Zhang et al., 1999; Wu et al., 2010).

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KEYWORDS

- **antiparasitic activity**
- **areca nut**
- **arecoline**
- **catechuins**
- **gastroprotective activity**
- **neuroprotective activity**
- **pyridine-type alkaloids**

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CHAPTER 78

Traditional Use, Chemistry, and Pharmacology of *Piper longum* L.

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78.1 INTRODUCTION

Piper longum L. [Syn.: *Chavica longa* (L.) H. Karst., *Chavica roxburghii* Miq., *Piper latifolium* W.Hunter, *Piper roxburghii* (Miq.) J.Presl, *Piper sarmentosum* Wall. and *Piper turbinatum* Noronha]. Vernacular names of this plant include gazpipal, pimpli, pipal, pipal mal, pipar, piplamul, pipli,

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pipli-mool (Hindi), capala, catikasira, chanchala, chupula, dantakapha, eranda, gonamika, granthika, kana, kanamula, kati, katubija, katugranthikam, kola, kolamula, kolya, korangi, krikala, krishna, krishnapippali, krsnatandula, kuna, magadha, magadhaja, magadhi, magadhodbhava, maghadi, pippali, pippali mula, pippalika, rudhakam, sadgranthi, sarvagranthikam, shaundi, shyama, sukshmatandula, sumulakam, syama, tandula, tiksnatandula, trikana, upakulya, ushuna, vaidehi, vaidehikana (Sanskrit), capala, cattu-tirpali, cattutirpali, chapala, cuttaterpati, kana, kattutipali, kattutippali, magadhi, pippali, tippali (Malayalam), alakalunku, alakalunku, alakaman, amirtai, ampu, arakanti, argadi, arippalam, arisi thippili, ariyantippilli, ariyappallam, arkali, arkati, arsithippili, arttikam, atcatti, atimaruntu, atti, calani, camilaki, camivaci, canam, capalai, capalatikam, caram, catevi, caucanti, cavuntai, cayalati, cayini, cayutai, cemmai, ceruppatai, cilettumanaci, cilettumanacini, cilettumattukkati, cukkumatantulam, dippili, ekalakikam, ekavacam, elivari, erantai, etakam, eytumalan, kakari, kakattiruppi, kalidi, kalini, kaman, kanai, kanam, kanamekampokki, kanamuli, kanavatai, kanna, kantankanam, kantumulam, kati, kattitosana, kattuttippilikkodi, keccarutti, kindigam, kirantiver, kirauncatanam, kirumanisattini, kirupantikam, kirusnam, kittinan, kola, kolagam, kolaiarukki, kotittippili, magadi, makati, malayaviretam, milagu, moti, motiver, mukattamancari, mukayi, narukkuttippili, narukkuveru, palappiratikam, panam, pipili, pippalai, piranciyapalam, pirapalam, ratintikam, takkolam, tanmantanmulam, tantapacalai, tantulam, tecavaram, thippili, thippiliver, thippli, tippilik kattai, tippilikkoti, tippilittavayam, tirantikam, titcanatantulam, tiyaipi, tiyonti, tulampikkiri, tulavi, tulavikam, tunavi, tuttan, ulakulam, ulavainaci, uncaram, upakilliyam, upakuliyai, upakuliyam, upakullikam, upakulliyai, usanai, utanai, uvakulam, vaitaki, vaitakikam, vaiteki, vanapippili, vatakunmanacini, vayateki, vayatorri, vettilai, viyalkana, viyalkanakam (Tamil), hipli, hippali, hippali balli, ippali, kuna, kuna balli, modi, thippali balli, tippili, yippali, yippilli (Kannada), pippallu, pippali (Telugu), pimpalee, pimpli, piplee, pipli (Marathi), dro-sman, dro-sman-narmo, na-le-sam, pi pi lin, pi pi lin gi rtsa ba (Tibetan), darfilfil, filfil daraz, pipal, pipal kalah, pipal kalan, pipal mol, pipla mul, pipla-mul, piplamul, pippala mul, pippali, rupa mukhi, tirkuta (Urdu), filfil-i-daraz, filfilderaz, filfildray, filfilmoya, maghz-pipal, pilpil, papal (Persian), dar filfil, dar-filfil, filfilmoya, filfilsiya, pila mol, piplamol (Arabic) and long pepper, Indian long pepper (English).

P. longum is a scandent or straggling shrub, sometimes ascending and climbing. Leaves to 8 × 4 cm, ovate, acute at apex, cordate, and strongly oblique at base, membranous, shining above; petiole 1–3 cm long. Female

spike stout, erect; peduncle 1.5 cm long; bracts peltate, orbicular. Male spike to 7 cm long, erect, slender; stamens 2. Berry 2 mm across, glabrous, black, or deep red. It is distributed globally in the Indo-Malesian region and Sri Lanka and is native to Northeast India. It has been recorded in India from the Central to Eastern Himalayan foothills, as well as the Western Ghats of Kerala and Tamil Nadu. It has also been recorded in Nicobar Island. The fruit and dried roots of *P. longum* is an important ingredient of Indian systems of medicine like Ayurveda, Sidha, and Unani. It is used in the prevention and treatment fever, diarrhea, piles, cough, hiccough, respiratory congestion, bronchial asthma, hoarseness of voice, consumption, flatulence, colic, vomiting, acid gastritis, edema, diseases of mouth, eye diseases, intrinsic hemorrhage, jaundice, and earache. Dried fruit powder of *P. longum* along with honey alleviates cough, dyspnoea, fever, splenomegaly, and hiccough.

78.2 PHYTOCHEMICAL CONSTITUENTS

The plant *P. longum* cover a wide range of chemical constituents ranging from alkaloids, terpenoids, steroids, flavonoids to glycosides and fatty acid (Foyer and Noctor, 2000; Yadav et al., 2020). The first report of piperine in *P. longum* along with piperlongumine and piperlonguminine was done by Chatterjee and Dutta (1966). Piperine alkaloid is the principal constituent in *P. longum*, yielded 3–5% from the plant. Chatterjee and Dutta (1967) obtained 16.58 mg/g piperine from the dried fruit of *P. longum*. Desai et al. (1988) reported some alkaloids from the roots of *P. longum* such as aristolactam AII, norcepharadione A, 2-hydroxy-1-methoxy-4H-dibenzo[de, g]qumoline-4,5(6H)-dione, cepharadione A, cepharanone B, piperolactam A, and glqumoline-4,5(6H)-dione. Madhusudhan and Vandana (2000) reported the occurrence of tetrahydropiperine from the extract of dried fruit of *P. longum*. Liu et al. (2009) reported turmerone, coumaperine, demethoxycurcumin, bisdemethoxycurcumin, aphanamol, N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine and 1-[1-oxo-5 (3,4-methylenedioxyphenyl)-2E-pentenyl]-pirrolidine from *P. longum*. Lee et al. (2010) reported novel alkamides from the fruit of *P. longum* includes, pipercide, retrofractamide C, dehydroretrofractamide C, pellitorin, guineesine, piperloein B, pipernonaline, and dehydropipernonaline. Dutta et al. (1975) isolated lignans such as sesamin, sylvatin, and diaeudesmin from the seeds of *P. longum*. The major flavonoids present in the fruits of *P. longum* includes quercetin, myricetin, kaempferol, catechin, epicatechin, apigenin, naringenin, and luteolin (Mustafa et al., 2010; Yadav et al., 2020).

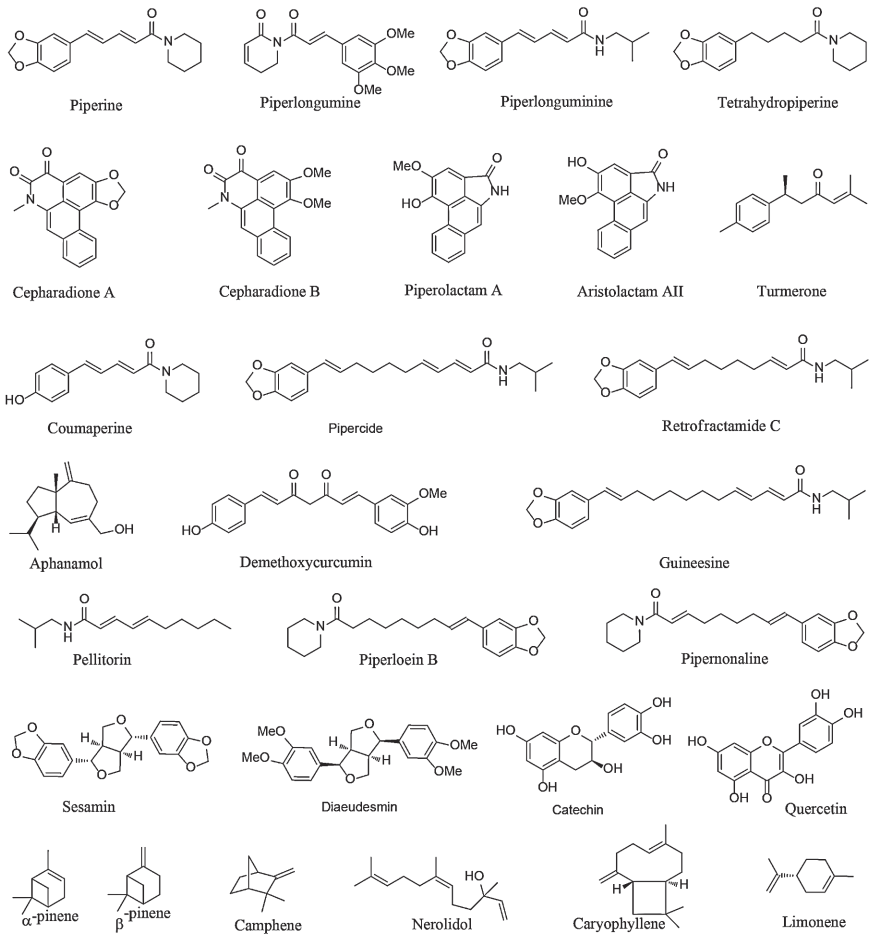
Varughese et al. (2016) reported the essential oil composition of root (62.0%), fruit (71.5%), stem (69.2%) and leaf (68.7%) of the *P. longum*. The oil composition of root, fruit, and stem (62.0%, 71.5%, and 69.2%), respectively and was dominated by the presence of monoterpene hydrocarbons while the leaf contain sesquiterpene hydrocarbons (68.7%) as the major components. The study led to the identification of 38 compounds from root, which mainly includes β-pinene (26.4%), camphene (13.9%), α-pinene (11.8%), bornyl acetate (10.0%), limonene (6.3%), δ-elemene (5.8%), caryophyllene (5.6%), pentadecane (5.0%), β-myrcene (1.5%), caryophyllene oxide (1.1%), and nerolidol (1.0%). In stem, 36 compounds were identified which mainly include β-pinene (34.8%), α-pinene (14.0%), limonene (10.3%), caryophyllene (9.3%), camphene (6.6%), bornyl acetate (5.0%), humulene (2.3%), nerolidol (2.2%), δ-elemene (1.6%), and 2-undecanone (1.0%). Total of 29 compounds were identified from the fruit, β-pinene (43.1%), α-pinene (15.3%), limonene (9.6%), nerolidol (8.8%), caryophyllene (5.7%), 2-undecanone (2.9%), 1-methylhexyl acetate (2.5%), β-myrcene (1.4%), and linalool (1.1%). Leaves contain 37 compounds, mainly nerolidol (22.5%), caryophyllene (16.8%), humulene (5.8%), gurjunene (2.6%), caryophyllene oxide (2.1%), 2-undecanone (2.0%), α-muurolene (1.8%), and δ-cadinol (1.9%). The principal components of fruit, root, and stem are α-pinene, β-pinene and camphene.

78.3 PHARMACOLOGICAL STUDIES

The biological properties of extracts, fractions, and isolated compounds from different parts of the *P. longum* are discussed in subsections.

78.3.1 ANTI-INFLAMMATORY ACTIVITY

The anti-inflammatory activity of dried fruit oil of *P. longum* (1 ml/kg) was evaluated in carrageenan-induced hind paw edema rat model. The oil significantly reduced the paw edema by 72.34% (Kumar et al., 2009). The cell adhesion molecules viz., intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin play an important role in controlling various inflammatory diseases. Kumar et al. (2005) isolated and characterized two compounds, ethyl 3′,4′,5′-trimethoxycinnamate and piperine from the combined hexane and chloroform extracts (CEs) of *P. longum* and evaluated the activities of these two compounds on tumor necrosis factor (TNF)-α induced expression of cell adhesion molecules by using primary



human umbilical vein endothelial cells (HUVECs). It was observed that both the compounds inhibited TNF-α induced expression of intercellular adhesion molecule-1 in a dose dependent manner. The compounds also blocked the adhesion of neutrophils to the endothelium in a time and concentration dependent manner. The protective effect of alkaloid fraction separated from *P. longum* was studied in dopaminergic neurons against inflammation induced damage by inhibiting microglial activation using lipopolysaccharide (LPS) induced dopaminergic neuronal damage in rats. Six weeks of treatment with the alkaloid fraction (50 and 75 mg/kg) significantly improved the survival rate of tyrosine hydroxylase-immunoreactive neurons in the substantia nigra pars compacta and dopamine levels in the striatum. The

alkaloid fraction also decreased the levels of TNF-α, interleukin 1β and interleukin 6. The excessive production of ROS and nitric oxide (NO) levels were also decreased. The over activated microglial cells were suppressed and the behavioral dysfunction induced by LPS were improved after the treatment (He et al., 2016).

Singh et al. (2008) reported that *P. longum* CE (17.5 μg/ml) inhibited the adhesion of neutrophils to endothelial monolayer by blocking TNF-α induced expression of cell adhesion molecules. This is mediated through nuclear factor kappa light chain enhancer of activated B-cells inhibition in endothelial cells. Lim et al. (2020) isolated retrofractamide C from *P. longum* and studied the anti-inflammatory effect of the compound in LPS induced J774A.1 cells and xylene induced mouse ear edema model. Administration of retrofractamide C (3 and 10 μM) decreased LPS induced NO and prostaglandin E2 secretion, and inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 expression. Retrofractamide C down-regulated LPS induced secretion of interleukin 1β and interleukin 6 and inhibited the phosphorylation of extracellular signal-regulated kinase and nuclear factor kappa B. The compound alleviated edema formation and inflammatory cell infiltration. The supercritical fluid from the fruits of *P. longum* showed potent anti-inflammatory activity by inhibiting LPS induced NO production in RAW264.7 macrophages (IC_{50} 38.5 μg/ml) compared to the standard drug indomethacin (Guoa et al., 2019). The anti-inflammatory property of the two varieties *P. longum* were compared by Kumari et al. (2012) in acute and sub-acute inflammatory models in albino rats. The *chhoti* variety of *P. longum* exhibited better suppression of paw edema compared to the *badi* variety. *Chhoti* variety suppressed both acute and subacute phase of inflammation. The anti-inflammatory effect of piperine (1-peperoyl piperidine) isolated from *P. longum* was scientifically validated in rats. The various acute and chronic models like carrageenan-induced rat paw edema, cotton pellet granuloma and croton oil induced granuloma pouch were employed (Mujumdar et al., 1990). The compound acted significantly in early acute changes in inflammatory process and chronic granulative changes. Piperine also acted partially through stimulation of the pituitary adrenal axis. Piperine inhibited the TNF-α induced expression of cell adhesion molecules by inhibiting nuclear factor kappa B activation in endothelial cells mediated via IκB kinase inhibition (Kumar et al., 2007).

The anti-neuroinflammatory effects of piperlongumine, an active component of *P. longum* was evaluated on LPS induced neuroinflammation using BV2 microglial cells. Pretreatment with compound (5 mM) significantly

inhibited the production of NO and PGE_2 induced by LPS. Piperlongumine (5 mM) suppressed the expression of iNOS, COX-2, TNF-α and IL-6. The compound at 5 mM dose significantly reduced luciferase activity of NF-κB and LPS-induced translocation of p65 suggesting the suppression of NF-κB signaling pathway (Kim et al., 2018). Bae et al. (2010) reported the inhibitory effect of piperine on LPS induced inflammatory responses. Piperine inhibited LPS induced endotoxin shock, accumulation of leukocyte and TNF-α production in TNF-α knockout mice. Piperine inhibited LPS/Poly(I:C)/CpG-ODN-(oligodeoxynucleotide) induced TNF-α production in peritoneal macrophages. Piperine inhibited interferon regulatory factor (IRF-1) level and phosphorylation and nuclear translocation of IRF-3. It also reduced the activation of signal transducer and activator of transcription. Sant'Ana et al. (2020), found that piperlongumine maintained pulmonary frequency, volume, and ventilation parameters similar to that of the normal control group, in an experimental model of respiratory inflammation resulting from cigarette smoke exposure in Balb/c mice. Piperlongumine administration recovered lung tissues and it increased the expression of AnxA1 and reduced COX-2, NF-κB and neutrophil elastase attenuating systemic and pulmonary inflammatory changes. Dichloromethane (DCM) fraction of *P. longum* (100 and 200 mg/kg) showed anti-inflammatory effect in cerebral ischemia model in rats by suppressing IL-1β, IL-6 and TNF-α expression levels. It also reduced oxygen free radicals and malondialdehyde (MDA) (Wang et al., 2017). Vijayarani et al. (2020) carried out a computational and pharmacokinetic study on the enhanced bioavailability of boswellic acid by *P. longum*. They have developed a co-administration strategy that facilitated the effective oral absorption and distribution of boswellic acid. *P. longum* extract (2.5 and 10 mg/kg) significantly increased the bioavailability of boswellic acid and cytochrome P_{450} mediated mechanism was involved in the increased bioavailability.

78.3.2 ANALGESIC AND ANTI-DEPRESSANT ACTIVITIES

Aqueous suspension of *P. longum* roots at 400 and 800 mg/kg doses exhibited significant non-steroidal anti-inflammatory drugs type of analgesia. The aqueous suspension at 800 mg/kg dose showed 50% protection against acetic acid-induced writhing in mice (Vedhanayaki et al., 2003). The intraperitoneal administration of piperine at 30, 50, and 70 mg/kg doses significantly inhibited acetic acid-induced writhing in mice. Piperine (30 and 50 mg/kg) showed a significant increase in the reaction time of mice in the tail-flick

assay. The results indicated the analgesic effect of piperine possibly mediated via opioid pathway (Bukhari et al., 2013). The methanolic fruit extract of *P. longum* and the secondary metabolite piperlongumine were evaluated for their analgesic and stress resistance increasing effects. After five days treatment, both of them showed dose dependent effects and exhibited doxycycline-like antidepressant activity in tail suspension test and aspirin-like analgesic effects in acetic acid-induced writhing test. Piperlongumine (4 mg/kg) and the methanolic fruit extract (16 mg/kg) suppressed foot shock stress-induced hyperthermia (Yadav et al., 2016). Mamun et al. (2011) investigated the central nervous system (CNS) depressant and analgesic properties of the methanolic extract (ME) of *P. longum* leaves. The extract showed dose-dependent CNS depressant effect compared to the standard drug diazepam. The leaf extract (200 mg/kg) exhibited significant analgesic activity and showed 57.58% writhing inhibition compared to the standard drug indomethacin (10 mg/kg). The formalin-induced pains in rats were also suppressed significantly by the extract. Piperlongumine (12.5 and 25 mg/kg) significantly decreased the immobility time in the forced swimming test but did not alter locomotor activity in the open field test, suggesting the anti-depressant-like effects of the alkaloid.

In chronic unpredictable stress model of depression, piperlongumine reversed both the decreased sucrose performance and increased immobility time in rats (Zhang et al., 2019). Mao et al. (2014) found that piperine isolated from *P. longum* reversed the effects of corticosterone on behavior and hippocampal brain-derived neurotrophic factor expression in mice. Piperine significantly suppressed behavioral and biochemical changes induced by corticosterone, suggesting the anti-depressant-like effect in corticosterone treated mice. Lee et al. (2005) reported the inhibitory effect of piperine isolated from *P. longum* on monoamineoxidases, MAO-A (IC_{50} 20.9 μM) and MAO-B (IC_{50} 7.0 μM). Kinetic analyzes revealed that piperine competitively inhibited MAO-A and MAO-B with K_i values of 19.0 ± 0.9 μM and 3.19 ±0.5 μM, respectively. It also reduced the immobility time in the tail suspension test without accompanying changes in ambulation when assessed in an open field suggesting the anti-depressant like activity of piperine. Li et al. (2007) reported the anti-depressant like effects of piperine in chronic mild stress treated mice. The drug (2.5, 5, and 10 mg/kg) reversed the damages induced by chronic mild stress by changes in sucrose consumption, plasma corticosterone levels and open field activity. It ameliorated the proliferation of hippocampal progenitor cells and brain-derived neurotrophic factor in hippocampus of mice was up-regulated by piperine treatment.

78.3.3 ANTIARTHRITIC ACTIVITY

Piperine exhibited antiarthritic activity in human interleukin-1β (IL-1β) stimulated fibroblast-like synoviocytes. It inhibited the expression of IL-6 and matrix metalloproteinase and decreased the production of PGE_2 in a dose-dependent manner. The compound also inhibited activator protein-1 into the nucleus in IL-1β treated synoviocytes and it significantly alleviated nociceptive and arthritic symptoms in rats (Bang et al., 2009). Yende et al. (2010) reported the antiarthritic activity of the aqueous extract of the fruits of *P. longum* in Freund's adjuvant-induced arthritic rats. The extracts (200 and 400 mg/kg) exhibited a significant reduction in paw swelling in rats. The results are supported by the radiographic analysis of the affected knees of rats. Ying et al. (2013) found that piperine inhibited IL-1β induced PGE_2 and NO production in human osteoarthritis chondrocytes. It further decreased the production of matrix metalloproteinase-3 (MMP-3), MMP-13, iNOS, COX-2 and NF-κB in human osteoarthritis chondrocytes. Piperlongumine isolated from *P. longum* fruits reduced the arthritic score and histopathologic lesion in collagen-induced arthritic mice. The compound also reduced the expression of serum anti-collagen II antibodies, TNF-α, IL-1β, IL-23, and IL-17 in human rheumatoid arthritis fibroblast-like synoviocytes (Sun et al., 2015). Piperlongumine suppressed dendritic cell maturation by the production of reactive oxygen species (ROS). The treatment with piperlongumine reduced LPS induced murine bone marrow derived dendritic cell maturation, characterized by the reduction in cluster differentiation CD80/CD86 expression, production of MCP-1, IL-12p70, IL-6, TNF-α, IL-23 and IFN-γ. It inhibited the activation of p38, JNK, NF-κB and P13K/Akt signaling pathways. The treatment improved the severity of arthritis and reduced splenic maturation of dendritic cells, collagen specific $CD4^+$ T-cell responses in collagen-induced arthritic mice (Xiao et al., 2016).

78.3.4 ANTIOXIDANT ACTIVITY

The ME of *P. longum* at a dose of 40 μg/ml exhibited potent antioxidant effect by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay (68.42%) compared to ascorbic acid standard (73.68%) and reducing power assay (Archana et al., 2015). Jagdale et al. (2009) evaluated the antioxidant effect of petroleum ether extract of the roots and piperine isolated from the roots of *P. longum*. Both showed a significant percentage of inhibition of free radicals, 74.12% and 72.13%, respectively. The petroleum ether extract and piperine treatment

decreased lipid peroxide levels and maintained the tissue glutathione (GSH) levels of isoproterenol-induced myocardial ischemia in rats. Reddy et al. (2014) studied the antioxidant effect of green synthesized silver nanoparticles by *P. longum* fruits. The aqueous fruit extract of *P. longum* and green synthesized silver nanoparticles showed potent antioxidant effects *in vitro*. Nakkala et al. (2016) reported the antioxidant and catalytic properties of green synthesized gold nanoparticles from *P. longum* fruit extract. Krishna et al. (2015) isolated apigenin 7,4′-dimethyl ether from the ethyl acetate (EAE) extract of *P. longum* fruits. The antioxidant effects were evaluated by total redox potential (196.03 μg/mg GAE), DPPH assay (IC_{50} 173.09 μg/ml), hydroxyl radical scavenging assay (IC_{50} 20.42 μg/ml) and enhanced superoxide dismutase (SOD) activity (25.3%).

78.3.5 ANTIMICROBIAL ACTIVITY

Piperine isolated from the dry roots of *P. longum* showed significant antibacterial effect against *Bacillus cereus* and *Escherichia coli* with maximum zone of inhibition (MIC value 12.5 μg/ml) (Lokhande et al., 2007). Reddy et al. (2001) found that piperlongumine (MIC 9 μg/ml), piperine (MIC 12.5 μg/ml) and pellitorine (MIC 20 μg/ml) isolated from *P. longum* were highly active against *Bacillus subtilis*, *Staphylococcus aureus* and *Bacillus sphaericus*. EAE fraction from *P. longum* fruit extract was found effective against *Mycobacterium smegmatis* (3,000 μg/ml) and *M. tuberculosis* (39 μg/ml). It also showed significant activity against *E. coli* (152 μg/ml), *Staphylococcus aureus* (14 μg/ml), *Salmonella typhi* (180 μg/ml), *Enterococcus faecalis* (15 μg/ml), and *Pseudomonas aeruginosa* (52 μg/ml) (Singh et al., 2011). The essential oil isolated from the fruits of *P. longum* possessed fungicidal property against some phytopathogenic fungi such as *Pyricularia oryzae*, *Rhizoctonia solani*, *Phytophthora infestans*, *Botrytis cinerea*, *Erysiphe graminis*, and *Puccinia recondita*. Pipernonaline, an alkaloid isolated from the hexane fraction of *P. longum* exhibited significant fungicidal activity against *Puccinia recondita* with 91% and 80% of inhibition at the doses 0.5 and 0.25 mg/ml, respectively (Lee et al., 2001).

78.3.6 ANTIAMOEBIC ACTIVITY

The ethanolic root extract of *P. longum* exhibited *in vitro* amoebicidal effect and cured 88% of caecal amoebiasis (Ghoshal and Lakshmi, 2002). The crude

methanolic extract of *P. longum* fruits showed antiamoebic activity against *Entamoeba histolytica* infecting the caecum of mice (Ghoshal et al., 1996). The treatment with the extract resulted in the decrease of the severity of caecal wall ulceration. The hexane, DCM, and MEs of *P. longum* fruits were tested *in vitro* against the growth of fresh isolates of the intestinal protozoan parasite *Blastocystis hominis* (Sawangjaroen and Sawangjaroen, 2005). The ethanolic extract (EE), hexane, and butanol soluble fraction showed *in vitro* amoebicidal effect (1,000 µg/ml) and the chloroform fraction exhibited the activity at 500 µg/ml. The EE and the compound piperine caused 90% and 40% of rats with caecal amoebiasis, respectively (Sawangjaroen et al., 2004).

78.3.7 ANTICANCER ACTIVITY

The fruit extract of *P. longum* and the isolated compound piperine exhibited antitumor activity. The extract was 100% toxic to Dalton's lymphoma ascites (DLA) (500 µg/ml) and Ehrlich ascites carcinoma (EAC) cells (250 µg/ml). Piperine was found to be cytotoxic to DLA, EAC, and L929 cells in culture. The extract (10 mg/kg) and piperine (1.14 mg/kg) inhibited solid tumor development in mice induced with DLA cells and there was an increase in the life span of mice (Sunila and Kuttan, 2004). Piperlongumine from *P. longum* selectively killed both solid and hematologic cancer cells, but not normal B-cells. SuHan et al. (2014) evaluated the effect of the compound on the proliferation and survival of B-cells acute lymphoblastic leukemia (B-ALL). There was a dose dependent inhibition of the proliferation of B-ALL, induced apoptosis and increased the expression of p21 in B-ALL cells through a p53 independent mechanism. *P. longum* EE selectively induced caspase independent apoptosis in tumor cells without affecting normal cells by targeting mitochondria leading to dissipation of the mitochondrial membrane potential and increased production of ROS. The *in vivo* studies revealed the antitumor effect of the extract in immune-compromised mice with colon cancer tumors. The hexane extract of *P. longum* showed 90.92% cytotoxic effects against human cancer cell lines (A549 lung, THP-1 leukemia, IGR-OVI-1 ovary and MCF-7 breast) and benzene extract displayed 84.87% cytotoxicity against MCF-7 breast, IGR-OVI-1 ovary and THP-1 leukemia cell lines (Ovadje et al., 2014; Sharma et al., 2014).

Piperlongumine exhibited synergistic anticancer effect with doxorubicin on DU-145 prostate cancer cells by inhibiting carbonyl reductase-1 (Piska et al., 2019). Piperlongumine induced ROS mediated apoptosis in human prostate cancer PC-3 cells in a dose dependent (30–90 µM) manner. The

compound upregulated the cleavage of procaspase-3/PARP and activated caspase-3 (Lee et al., 2013). Rawat et al. (2020) reported the anti-neoplastic potential of piperlongumine against human intestinal carcinoma *in vitro*. The compound inhibited cell proliferation of INT-407 and HCT-116 cells in a dose dependent manner. The increased intracellular ROS level by the compound resulted in oxidative stress, mitochondrial dysfunction and nuclear fragmentation. It up-regulated p53, p21, BAX (bcl-2 associated X protein), and SMAD4, and down-regulated Bcl-2 and Survivin. Piperlongumine increased the apoptotic effect of doxorubicin and paclitaxel in HeLa cervical cancer cell line (Seber et al., 2020). Piperine inhibited canonical Wnt pathway induced by the overexpression of β-catenin, β-catenin-S33A or dnTCF4VP16 and suppressed β-catenin nuclear localization in HCT-116 cell line. The compound impaired cell proliferation and migration in HCT116, SW480 and DLD-1 colorectal tumor cell lines (Almeida et al., 2020). Piperlongumine loaded nanoparticles inhibited the growth, migration, and invasion and epithelial-to-mesenchymal transition of triple-negative breast cancer cells (Ghassemi-Rad et al., 2021). Piperlongumine interfered with several stages of T-cell activation and inhibited Tcell/APC immune synapse formation, co-stimulation induced upregulation of CD69 and CD25. T-cell proliferation and secretion of proinflammatory cytokines. It increased intracellular ROS and decreased GSH in human peripheral blood T-cells. The compound predominantly inhibited T_H17-related genes and differentiation in to T_{reg} cells was increased by the treatment. Thus, it can act as an immunosuppressant by exerting pro-oxidative effects (Liang et al., 2020). Piperlongumine induced cell cycle arrest via ROS accumulation and IKK-β (Inhibitor of nuclear factor Kappa-B kinase) suppression in MCF-7 human breast cancer cell lines. The compound inhibited proliferation of MCF-7 in a dose dependent manner (10–40 μM) compared to the control and suppressed cell proliferation through G2/M cell cycle arrest. The expression cyclin B1, cyclin D1, cyclin dependent kinase-1 (CDK1), CDK4, CDK6 and proliferating cell nuclear antigen (PCNA) expression levels were significantly decreased in piperlongumine treated cells. The compound attenuated the nuclear translocation of NF-κB p65 by decreasing IκBα phosphorylation as well as the expression IKK-β (Jeongy et al., 2019).

Piperlongumine selectively inhibited the cell growth of human ovarian cancer cells and induced cell apoptosis G2/M phase cell cycle arrest and intracellular ROS accumulation in a dose dependent manner. The compound induced apoptosis and synergized with cisplatin or paclitaxel in human

ovarian cancer cells (Gong et al., 2014). The treatment with piperine in combination with thymoquinone resulted in regression of breast carcinoma syngraft with a clear synergistic antiproliferative interaction with CI value 0.788. There was a significant decrease in tumor size. The combination therapy resulted in a significant decrease in vascular endothelial growth factor (VEGF) expression, and it induced high degrees of apoptosis and necrosis in tumor cells (Talib, 2017). Wang et al. (2015) reported the potent anti-neoplastic effect of piperlongumine against human lung cancer A549 cells by inducing apoptosis and autophagy. The compound inhibited phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR (mammalian target of rapamycin) pathway. It inhibited the growth of A549/DTX xenograft tumors by inhibiting cell proliferation, apoptosis induction and decreased expression of p-Akt and p-mTOR in tumor xenograft tissues. Piperlongumine induced biliary cancer cell death by induced ROS production and cell cycle arrest in intrahepatic cholangio carcinoma cells (HuCCT-1) and gall bladder cancer cells (OCUG-1) cells by causing G2/M cell cycle arrest in HuCCT-cells and G0/G1 cell cycle arrest in OCUG-1 cells (Chen et al., 2019). Piperlongumine promoted pro-death of retinoblastoma cell lines WERI-kb and Y79. The compound (10 μM) significantly inhibited cell growth decreased the levels of cyclins and CDK1 and increased CDKN1A and triggered caspase-3 independent cell death process by ROS production (Pillet et al., 2021). Piplartine and piperine, two alkaloid amides isolated from *P. longum* exhibited cytotoxic effects towards sarcoma-180 bearing mice. The compounds inhibited solid tumor development at the rate of 52.3% and 56.8%, respectively for piperine and piplartine (Bezerra et al., 2006). Jafri et al. (2019) reported apoptotic potential of piperine in human cervical adenocarcinoma via ROS mediated mitochondrial pathway and caspase-3 activation. Piperine inhibited the growth of HeLa cells with increased ROS production and nuclear condensation and associated with G2/M phase cell cycle arrest. The compound encouraged cell death by the loss of MMP, DNA fragmentation and caspase-3 activation. Piperine inhibited B16F-10 melanoma cells induced lung metastasis in C57BL/6 mice and the compound significantly reduced (95.2%) tumor nodule formation (Abdubakiev et al., 2020). There was a significant reduction in lung collagen hydroxyl proline and uronic acid in piperine treated group. Piperine significantly reduced lung hexosamine content (Pradeep and Kuttan, 2002). *P. longum* showed cell cycle inhibitory activity in A549 cells and protection against metal induced toxicity in rats (Amit et al., 2014).

78.3.8 IMMUNOMODULATORY ACTIVITY

The administration of *P. longum* fruit alcoholic extract and piperine increased the total white blood cells count, plaque forming cells, bone marrow cellularity and α-esterase positive cells in DLA and EAC induced tumor bearing mice (Sunila and Kuttan, 2004). Bernardo et al. (2015) evaluated the effect of piperine to B-cell functioning and on humoral immune response to T-independent antigens *in vitro*. The compound inhibited LPS and immunoglobulin αIgM induced proliferative response, IgM antibody secretion and reduced the expression cluster differentiation CD86. Piperine in combination with gamma aminobutyric acid (GABA) mediated p38 and Jun N-terminal kinases (JNK) p38 mitogen activated protein kinases (MAPK) activation, which elevated erythropoietin (EPO) and erythropoietin receptor (EPO-R) expression resulting in the up-regulation of IL-10 and NF-κB (Lee et al., 2018). Kumar et al. (2015) and Anoop et al. (2015) evaluated the binding affinity of piperine to immune cell receptors and its protective effects on deltamethrin induced immunotoxicity *in vitro*. The docking results showed that piperine showed binding affinity towards CD4 and CD8 receptors. Piperine (1, 10, and 50 μg/ml) increased cell viability in a dose dependent manner and it also reduced deltamethrin induced ROS and caspase-3 activation. The aqueous and ethanol extracts of *P. longum* fruits (250 μg/ml) exhibited 100% giardicidal effect against giardiasis caused by *Giardia lamblia*. The survival of trophozoites in mice was observed as 11.12, 8.54, and 5.81 for fruit powder, aqueous, and ethanol extracts, respectively and it was comparable to the control group. The extracts possessed both specific and non-specific immunostimulatory activity as evident from the results of hemagglutination antibody titer, plaque forming cell counts, phagocytic index and macrophage migration index (Tripathi et al., 1999). An Ayurvedic preparation, 'Pippali Rasayana' containing *P. longum* as the main ingredient, was evaluated by Agarwal et al. (1994) for its anti-giardial and immunostimulatory activity in mice infected with *Giardia lamblia* trophozoites. The drug induced significant activation of macrophages as evidenced by the increased phagocytic activity and macrophage migration index. Piperinic acid isolated from *P. longum* exhibited a dose dependent decrease of CD4+ and CD8+ T-cells and cytokine levels in sensitized Balb/c mice with a marked inhibition at 40 mg/kg. Piperinic acid (5 μg/ml) inhibited mitogen induced peripheral blood mononuclear cells (PBMCs) proliferation, Concanavalin-A (Con-A) induced TNF-α and LPS induced IL-1β and iNOS under *in vitro* conditions (Devan et al., 2007).

78.3.9 ANTIDIABETIC AND ANTI-HYPERLIPIDEMIC ACTIVITIES

The antidiabetic and anti-hyperlipidemic effects of *P. longum* root aqueous extract was evaluated in streptozotocin (STZ)-induced diabetic rats. The extract (200 mg/kg) showed significant antidiabetic effect after 6 h of the treatment. There was a significant decrease in fasting glucose levels and liver markers in diabetic rats (Nabi et al., 2013). Kumar et al. (2013) investigated the antidiabetic and antihyperlipidemic activities of extracted oil and piperine from *P. longum*. The oil and piperine administered groups showed significant increase in body weight, plasma insulin, liver glycogen content and high-density lipoprotein (HDL) levels and decrease in glycosylated hemoglobin, total cholesterol (TC) and triglyceride levels compared to the control group. The α-glucosidase, aldose reductase and pancreatic lipase inhibitory effects were determined and the IC_{50} values were found to be 150 ± 2.5, 120 ± 1.2, and 175 ± 1.2 µg/ml, respectively. Manoharan et al. (2007) evaluated the antihyperglycemic and anti-lipid peroxidation (LPO) properties of *P. longum* dried fruits EE in alloxan induced diabetic rats. The extract corrected the alteration observed by the activities of carbohydrate metabolizing enzymes such as glucose-6-phosphatase (G6Pase), hexokinase (HK), glucose-6-phospahte dehydrogenase, fructose 1,6-biphosphatase and glycogen phosphorylase in diabetic rats. Chaurasia and Das (2012) reported the antihyperglycemic activity of the ethanolic root extract of *P. longum* in alloxan-induced diabetic mice. There was a significant decrease in blood glucose levels with improved lipid profile in diabetic mice. The glycogen content and serum insulin levels were also improved in extract treated groups compared to the control.

Atal et al. (2016) found that the combination of piperine (10 mg/kg) and metformin (250 mg/kg) exhibited significant blood glucose lowering effect as compared to metformin alone on both 14th and 28th day of the treatment. Vyas and Vyas (2020) reported the hypoglycemic activity of the EE of the leaves of *P. longum* (100, 200, and 400 mg/kg) in alloxan-induced diabetic rats. An *in-silico* study involving the major reported compounds such as piperine, piperlongumine, piperlonguminine, and retrofractamide A from *P. longum* were screened and analyzed for the antidiabetic activity by observing the interaction of the compounds with the receptors via molecular docking technique. The study revealed that these four compounds can act as inhibitors for dipeptidyl peptidase-4, glucokinase regulatory protein (GKRP), glutamine-fructose-6-phosphatase transaminase-1,11-β-hydroxysteroid dehydrogenase type-1 and protein tyrosin phosphatase 1β, which support the

glucose digestion and increment insulin affectability (Thakuria et al., 2020). Verma et al. (2017) reported the hypolipidemic property of EE of *P. longum* fruits in an acute model of hyperlipidemia in rats. The extract (500 mg/kg) significantly reduced TC, triglyceride, and phospholipid levels and reactivated post heparin lipolytic activity. In cholesterol rich-high-fat-diet induced chronic model of hyperlipidemia, there was a significant decrease in the lipid profile was observed along with an increase in post-heparin lipolytic activity. Bao et al. (2012) studied the hypolipidemic effects of piperine derivative GB-N isolated from *P. longum* in high fat diet (HFD)-fed rats. The serum triglyceride level was significantly decreased with an increase in HDL levels. The treatment with GB-N (10 mg/kg) up-regulated the levels of hepatic β-hydroxy β-methylglutaryl-CoA (HMG)-CoA reductase, Cytochrome P_{450} family 7 subfamily-A member 1 (CYP7A1), Lecithin–cholesterol acyltransferase and low-density lipoprotein receptor expression. Kharbanda et al. (2016) isolated piperine and hydrolyzed under basic condition to obtain piperic acid. This compound was used as the precursor for the synthesis of 20 piperine derivatives containing benzothiazole moiety. These derivatives were evaluated for antidiabetic activity on STZ-induced diabetic model and nine of the 20 novel piperine analogs exhibited potent antidiabetic effects compared to the standard rosiglitazone. These derivatives were also evaluated for their action as peroxisome proliferator-activated receptor (PPAR)-γ agonists.

Atal et al. (2012) evaluated the antidiabetic effect of piperine in alloxan-induced diabetic mice. The results of the sub-acute study revealed the significant blood glucose level lowering effect of piperine (20 mg/kg). Piperine (10 mg/kg) significantly increased the dose dependent anti-hyperglycemic effect of nateglinide in alloxan-induced diabetic animals. The study demonstrated that piperine could be used as a potential bioenhancer along with nateglinide (Sama et al., 2012). The bioassay-guided fractionation and isolation of fruit EE of *P. longum* yielded the compounds such as piperlonguminine, piperine, and pipernonaline as the main anti-hyperlipidemic compounds exhibiting significant *in vivo* anti-hyperlipidemic effect comparable to the standard drug simvastatin (Jin et al., 2009). GB-N, a thermostable form of piperlongumine from *P. longum* dose dependently reduced TC level in HepG2 cells and low-density lipoprotein receptor gene expression was up-regulated (Bao and Borjihan, 2012). GB-N dose dependently reduced serum TC, LDL-cholesterol, and triglyceride levels and increase HDL levels in diet induced hyperlipidemic rats. Song et al. (2014) investigated the inhibitory effect of piperlonguminine on human cytochrome P_{450}. The compound significantly

inhibited cytochrome P_{450} family-1 subfamily-A member-2 mediated phenacetin O-deethylation with IC_{50} 8.8 μM, as nicotinamide adenine dinucleotide phosphate independent inhibition. Shah et al. (2011) studied the effect of piperine in the regulation of obesity induced dyslipidemia in HFD-fed male Sprague Dawley rats. The compound reduced the levels of TC, triglycerides, low density lipoprotein, very low-density lipoprotein and fat mass. The comparative effects of piperine and simvastatin were studied on hepatic steatosis in hyperlipidemic rats. Piperine and simvastatin significantly reduced the accumulation of triglycerides, cholesterol, and lipid peroxides in the liver. The activities of serum amino transferase and alanine transferase were significantly deceased, and SOD was increased. Piperine (5 mmol/l) showed inhibitory effect on pancreatic lipase *in vitro* (Tunsophon and Chootip, 2016).

78.3.10 NEUROPROTECTIVE ACTIVITY

P. longum alkaloids were tested for the neuroprotection effects in MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) induced Parkinson's disease model. The alkaloid fraction (60 mg/kg) significantly increased total movement time and distance, increased dopaminerigic levels, 3,4-dihydroxyphenyl acetic acid, GSH, and SOD and decreased the levels of LPO of MDA (Bi et al., 2015). Subramanian et al. (2010) reported the neuroprotective effect of *P. longum* in C6 Glioma induced rats. Treatment with *P. longum* extract (20 mg/kg) significantly attenuated the increased levels of lipid peroxides, lactate dehydrogenase, 5′-nucelotidase, creatine kinase and acetylcholine ester indicated the protective effect in glioma induced rats. DCM fraction of *P. longum* markedly inhibited ischemia-induced cellular damage in rats. Results of immunohistochemical analysis revealed that the expression of α-sym reduced and the expression of post synaptic density protein (PSD-95) and syn-1 protein increased. The fraction treated group showed increased PSD-95, calmodulin, calcium/calmodulin activated protein kinase and N-methyl D-aspartate receptor subtype 2B (Hua et al., 2019a). Hua et al. (2019b) studied the effects of piperine on neuronal apoptosis in peri-infarcted cerebral cortices of rats with permanent middle cerebral artery occlusion injury. The results showed that piperine administration caused markedly decreased neurological deficit, less ischemia-induced cellular damage with less severe micro and macro-cellular cerebral structural changes. The expression of caspase-3, caspase-9 and cyt-c are also

inhibited significantly. It was found that piperine and piperlonguminine caused an improvement in rotenone-induced motor deficits. The treatment reduced ROS production and mitochondrial permeability was inhibited. The compounds stimulated autophagy, likely mitigating neuronal damage by the removal of damaged mitochondria (Wang et al., 2016).

Zhang et al. (2020) evaluated the effect of DCM extract of *P. longum* in mitigating ischemic stroke by activating the Akt/mTOR signaling pathway to suppress autophagy. The treatment caused the reduced infarct volume, neurological score and brain damage. The therapy caused the downregulation Ats and phosphorylated-serine 473-AKT expression and up-regulation. An appropriate concentration of piperine effectively inhibited the synchronized oscillation of intracellular calcium levels in the hippocampal neuronal networks of rat and repressed spontaneous synaptic activation. The treatment also exhibited a protective effect on glutamate induced decrease of cell viability and apoptosis of hippocampal neurons. The results indicated that the neuroprotective activity of piperine was associated with the suppression of synchronization of neuronal networks, Ca^{2+} overloading and presynaptic glutamic acid release (Fu et al., 2010). Yang et al. (2015) reported the neuroprotective property of piperine on MPTP-induced Parkinson's disease in mice. Piperine prevented MPTP-induced decrease in the number of activated microglia, oxidative stress and expression of IL-1β. Piperine exhibited a protective effect on dopaminergic neurons. Alkaloids extracted from *P. longum* showed a protective effect on dopaminergic neurons against inflammatory damage by inhibiting microglial activation in LPS-induced dopaminergic neuronal damage in rats. The treatment with alkaloids resulted in an improvement of survival rate of tyrosine hydroxylase-immunoreactive neurons in the substantia nigra pars compacta and dopamine levels in the striatum. The inflammatory cytokines TNF-α, IL-6 and IL-1β were decreased and the overacting microglial cells were suppressed by the treatment.

78.3.11 HEPATOPROTECTIVE ACTIVITY

Piperine from *P. longum* showed significant protection against tert-butyl hydroperoxide and carbon tertrachloride induced hepatotoxicity. The compound significantly reduced LPO, enzymatic leakage of alkaline phosphatase (ALP) and alanine transaminase from hepatocytes and prevented the depletion of GSH levels in mice. The *in vivo* results were comparable to the standard drug silymarin (Koul and Kapil, 1993). The hepatoprotective activity of *P. longum* fruit extract reduced $AlCl_3$-induced hepatotoxicity as

evident from the reversed enzyme levels of ALP, serum glutamine oxaloacetic transaminase, serum glutamic pyruvic transaminase (SGPT) activities as well as bilirubin and creatine levels. Piperine inhibited LPO (Sharma et al., 2014). Jalalpure et al. (2003) evaluated the hepatoprotective activity of *P. longum* fruits in CCl_4 intoxicated rats. The ethanol extract (300 mg/kg) and butanol fraction (300 mg/kg) showed significant protective effect by lowering the hepatic enzymes compared to the standard Liv52. *P. longum* traditional milk extract exhibited hepatoprotective activity against CCl_4 induced liver toxicity in Wistar rats. The extract (200 mg/kg) showed significant effect as evident from the decreased serum enzyme levels, total bilirubin and direct bilirubin compared to silymarin (Patel and Shah, 2009).

Sabina et al. (2010) found that piperine attenuated acetaminophen-induced hepatotoxicity in mice. Piperine (25 mg/kg, i.p) treatment resulted in a significant decrease in liver marker enzymes, TNF-α and LPO products with an increase in antioxidant status. Piperlongumine attenuated bile duct ligation induced liver fibrosis in mice via the inhibition of transforming growth factor (TGF-β1)/Smad (SMAD protein) and epithelial-mesenchymal transition (EMT) pathways. The pathological conditions were reversed by the treatment. It also inhibited hepatic stellate cells activation and extracellular matrix deposition via down-regulation of fibronectin, α-SMA (smooth muscle actin) and collagen 1a expression in the fibrotic liver. Piperlongumine inhibited significantly TGF-β1/Smad and EMT signaling pathways (Chilvery et al., 2020). The treatment with the ethanol extract of *P. longum* inhibited CCl_4 induced liver fibrosis. The treatment resulted in a significant decrease of hydroxyl proline level. Christina et al. (2006) evaluated the inhibitory effect of *P. longum* extract against carbon tetrachloride induced liver fibrosis and the extract significantly reduced the hydroxyl proline level.

78.3.12 CARDIO-PROTECTIVE ACTIVITY

The methanolic fruit extract of *P. longum* was evaluated for the cardioprotective activity against Adriamycin (ADP)-induced cardiotoxicity in Wistar rats. Pretreatment with the extract (250 and 500 mg/kg) ameliorated the toxic effects induced by ADP on lipid peroxide formation. The extract restored the activities of marker enzymes. The extract treatment increased the activity of antioxidant enzymes like SOD, catalase (CAT), GSH reductase, GSH peroxidase along with reduced GSH. Histopathological studies showed that the pretreatment with the extract reduced the intensity of ADP induced

degenerative changes in cardiac tissues suggesting the cardioprotective effect of *P. longum* (Alok et al., 2008). Iwashita et al. (2007) examined the effects of various extracts of *P. longum* in rabbit platelet function. The ethanol and butanol extract inhibited rabbit platelet aggregation through antagonizing thromboxane A2 receptor. The extract also inhibited phosphoinositide hydrolysis induced by U46619 ($C_{21}H_{34}O_4$). Shoji et al. (1986) reported the coronary vasorelaxant activity of an amide dehydropipernonaline, isolated from *P. longum* fruits. Park et al. (2007) studied the anti-platelet effect of four acidamides namely piperine, pipernonaline, piperoctadecalidine, and piperlongumine isolated from *P. longum* fruits. The antiplatelet effects were examined on washed rabbit platelet aggregation. All the four compounds showed dose dependent inhibitory effect on washed rabbit platelet aggregation induced by collagen platelet activating factor and arachidonic acid.

78.3.13 GASTROPROTECTIVE ACTIVITY

The water decoction of *P. longum* (50 mg/kg) was studied for its antiulcer effects in rats. The decoction showed a significant protective effect against gastric ulcers induced by 2 h cold resistant stress, aspirin (200 mg/kg) and 4 h pylorus ligation. The protective effect seemed to be due to the augmentation of mucin secretion and decreased cell shedding rather than offensive acid and pepsin secretion (Agrawal et al., 2000). Ononiwu et al. (2002) reported the effects of piperine on gastric secretion in albino rats. It showed significant dose dependent increase in gastric secretion compared to the control. About 20 mg/kg produced a 22.2% increase and the highest dose employed in the study (142 mg/kg) produced 334.6% increases in the gastric acid secretion. The increased acidity induced by piperine may be due to its stimulatory effect on histamine H2 receptors. Piperine at doses of 25, 50, and 100 mg/kg protected the experimental animals from gastric ulceration in a dose dependent manner. The inhibitory rats were 16.9, 36.0, and 48.31% in stress ulcers; 19.2, 41.5, and 59.6% in hydrochloric acid ulcers, 44, 51.1, and 64.4% in indomethacin ulcers and 4.8, 11.9, and 26.2% in pyloric ligation ulcers. The compound inhibited gastric juice volume, gastric acidity and pepsin A activity (Bai and Xu, 2000).

78.3.14 ANTI-ALLERGIC ACTIVITY

Piperine (10, 20, and 40 mg/kg, p.o) showed significant dose dependent protection with respect to nasal rubbing, redness of nose and sneezing after

the nasal challenge. There was a dose dependent decrease in histamine and NO level of piperine treated group. The expression of IL-6, IL-1β and immunoglobulin IgE were also reduced compared to the control group. Piperine significantly reduced mast cell degranulation and ovalbumin induced paw edema in rats compared to the control group (Aswar et al., 2015). Kaushik et al. (2012) carried out the antihistaminic and anti-asthmatic studies of the petroleum ether, alcohol, and decoction of *P. longum* fruits. The *in vitro* study was carried out using Guinea pig ileum, histamine induced bronchospasm study carried out in Guinea pigs and haloperidol induced catalepsy in mice. The extract (100 µg/ml) exhibited significant inhibition of the histamine induced contraction of isolated Guinea pig ileum. The extract at doses of 50, 100, and 200 mg/kg exhibited significant effect against histamine-induced bronchospasm, haloperidol induced catalepsy and passive paw anaphylaxis. The petroleum ether extract and decoction (200 mg/kg) showed a significant decrease in a number of leukocytes in milk-induced leukocytosis study.

78.3.15 ANTI-OTOTOXICITY ACTIVITY

P. longum EE showed protection against gentamicin-induced hair loss in neonatal cochlea cultures. The extract exhibited significant dose dependent activity against gentamicin induced hair loss. The extract also showed NO radical scavenging effect. The study indicated the therapeutic efficacy of *P. longum* for the management of gentamicin-induced ototoxicity (Du et al., 2012; Yadav et al., 2014).

78.3.16 ANTI-FERTILITY ACTIVITY

The crude extract and different fractions extracted from the fruit powder of *P. longum* showed anti-fertility effect in female rats. The crude extract and hexane fraction showed 100% and 86% effect, respectively (Lakshmi et al., 2006).

78.3.17 BIOAVAILABILITY ENHANCING PROPERTY

The bioavailability of structurally and therapeutically diverse drugs was enhanced by piperine by modulating membrane dynamics. It is due to the partitioning and increased permeability of piperine. The effect is attributed to increased absorption which led to cause alterations of the lipid dynamics of the membrane and conformational changes of enzymes in the intestine.

The compound also reported to enhance the oral bioavailability of phenytoin in humans (Kumar et al., 2011).

78.3.18 TOXICITY STUDIES

Acute (0.5, 1.0, and 3.0 g/kg) and chronic (100 mg/kg) toxicity studies of EE of *P. longum* fruits were carried out in mice. The extract caused no significant acute or chronic mortality compared to the control (Shah et al., 1998). Piperine showed acute toxicity to mice, rats, and hamsters. The LD_{50} values for a single intravenous (i.v), intraperitoneal (i.p), intragastric (i.g) and intramuscular (i.m) administration of piperine to adult male mice were determined as 15.1, 43, 200, 330, and 400 mg/kg, respectively (Piyachaturawat and Toskulkao, 1983).

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KEYWORDS

- **Indian long pepper**
- **piperine**
- **essential oil**
- **beta-pinene**
- **anti-inflammatory activity**
- **anticancer activity**
- **bioavailability enhancer**

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CHAPTER 79

Pharmacology and Bioactivities of Lesser Galangal (*Alpinia officinarum* Hance): A Brief Review

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79.1 INTRODUCTION

According to the proverb "Food is a medicine and medicine is food," we all missed to focus on traditional medicinal plants. The majority of plants have pharmacological effects and medicinal values but are not appropriately identified. One such plant is *Alpinia officinarum*. Its common name is lesser galangal. It belongs to the ginger family (Zingiberaceae) and comprises several local names like southern ginger; Indian root and China root (Lin et al., 2015). Since it belongs to the Zingiberaceae family, it propagates through rhizome; besides being a medicinal plant, it too has a pleasing aroma, so it also comes under aromatic plants. *A. officinarum* is a perennial plant that completes its life cycle in more than two years. Its rhizome is brown, and it flourishes to a stem height of 100–150 cm. It prefers primarily moist soil and environment to grow well (Abubakar et al., 2018). The roots are adventitious and possess several fiber-like structures; stems are in aerial portions with leafy structures. The flowers are usually complete, bisexual, and have three petals with yellowish-white color. Fruits are capsules, and they possess numerous tiny seeds which are endospermic and aromatic (Naing et al., 2019). A study from several researchers showed that *A. officinarum* has

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medicinal properties, and it exhibits antioxidant, anti-inflammatory, anti-ulcer, and anti-diarrheal properties. For several 100 years, the dried rhizome has been used to treat cold, cough, ulcer, and stomach-related disorders (Ding et al., 2019). The roots of *A. officinarum* hold galangin, alpin, volatile oils, synthetic, and bioactive compounds. Antitumor, antibacterial, and antifungal activity are noted in bioactive compound galangin (Zhang et al., 2010).

Alpinia officinarum rhizome samples were subjected to elemental analysis. The copper, zinc, and magnesium concentration shifted in various samples, whereas chromium remained the lowest (0.680 ppm). The various other mean elemental concentration recorded in the *A. officinarum* rhizomes in (ppm) are as follows: Cr – 0.680; Mn – 72.30; Fe – 85.50; Ni – 21.02; Cu – 0.753; Zn – 9.331; Mg – 569.5; Ca – 438.8; Na – 152.8; and K – 3,570 ppm. *Alpinia officinarum* has lipid percentage which are vital factors that determines pharmacopeial constants (Alasmary et al., 2019).

79.2 BIOACTIVES

Since all these plant species have medicinal properties, many bioactive compounds are reported; *Alpinia* species have about 17 monoterpenoids, 132 sesquiterpenoids, 143 diarylheptanoids, and stands first out from all the plants in the Zingiberaceae family in the amount of diterpenoids contents available in the plant. Monoterpenoids are classified into rubarine, sumadain C and isorubarine (Ma et al., 2017). *A. officinarum* contains several bioactive compounds like (4E)-1,7-diphenyl-4-en-3one Diarylheptanoid was extracted from *A. officinarum* rhizome. It contains flavonoids, sesquiterpenes, and glycosides. The detailed study on this plant showed still more bioactive compounds obtained from dimeric diarylheptanoids; they are alpinin D, alpinin C, alpinin B, 1,7-diphenyl heptane, heptan-3-one, and so on (Abubakar et al., 2018). The research conducted by Naing et al. (2019) reveals that *A. officinarum* consists of tannins, phenolic compounds and alkaloids. Primary bioactive compounds like quercetin, isorhamnetin, apigenin, and rhamnocitin are noted. *A. officinarum* contains essential oils (EOs) like camphor (3.4%), carotol (8.9%), α-teripineol (0.7%), α-eudesmol (4.5%), and β-pinene (3.1%). The bioactive compounds, EOs, and decoction/powder can successfully treat vomiting sensations, nasal infections and seasickness. *A. officinarum* purify the air and its surrounding environment (Ding et al., 2019). Few compounds of *A. officinarum* are listed in Figure 79.1.

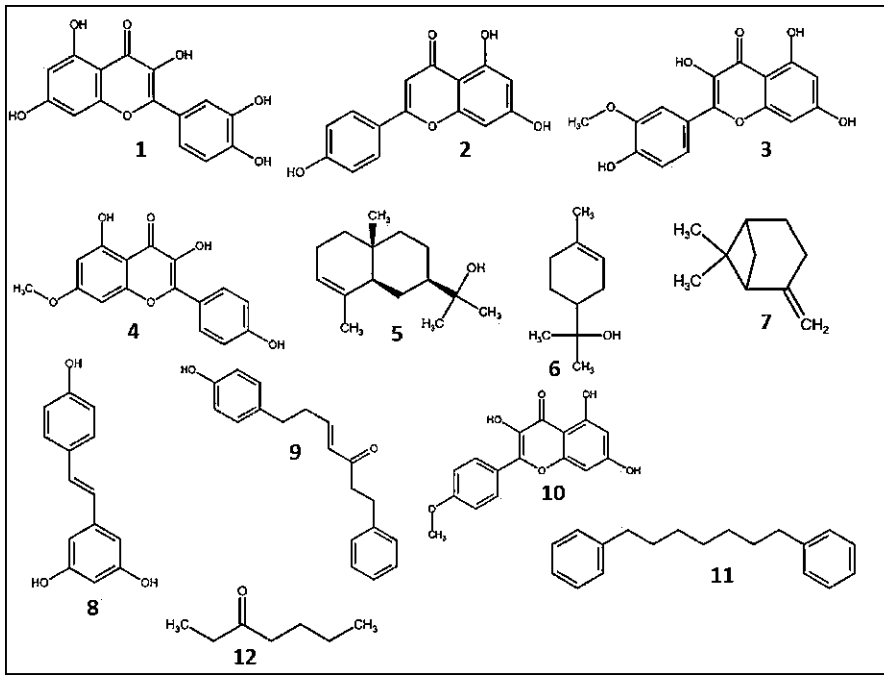


FIGURE 79.1 Few compounds of *A. officinarum*. (1) Quercetin; (2) apigenin; (3) isohamnetin; (4) rhamnocitin; (5) α-eudesmol; (6) α-teripineol; (7) β-pinene; (8) resveratrol; (9) 7-(4-hydroxyphenyl)-1-phenyl-4E-hepten-3-one; (10) kaempferide; (11) 1,7-diphenylheptane; and (12) heptan-3-one.

Source: Marvin 17.21.0, ChemAxon tool was used for drawing chemical structures.

79.3 PHARMACOLOGY

79.3.1 ANTIDEPRESSANT ACTIVITY

Stress is one of the severe effects in recent days, which affects humans both physically and mentally. In a study, *A. officinarum* proves to control depression by controlling the neuroprotective functions. The plant extract is prepared from 1,000 grams of dried rhizome, dissolved in ethanol (70%) and prepared in three different dose levels 50, 100, 150 mg/kg. BALB mice weighing 25–30 g was taken and segregated into four groups; one is fed with normal saline remaining 2, 3, and 4 with *A. officinarum* extracts of different doses; the animal models were subjected to stress by forcing them to force swim test, rotarod test and tail suspension test. After 21 days of analysis, the mice fed with plant extracts of 50 mg/kg, 100 mg/kg showed

a reduced immobility time and other factors responsible for stress. They showed increased TCA levels in the brain, showing that *A. officinarum* has antidepressant activity (Salehi et al., 2020).

79.3.2 ANTI-INFLAMMATORY ACTIVITY

A. officinarum bioactive compounds can treat inflammation, which is confirmed by a study on plant extracts. Methanolic *A. officinarum* plant extract was prepared at different dose levels. The female Wistar rats (150–200 g) of 10–12 weeks were chosen. The rats were divided into different groups; the rats had paw induced edema by injecting with carrageenan. Group one was treated with 0.1% of CMC and another group with diclofenac as a standard drug. The remaining groups were fed with methanolic extract of *A. officinarum* with different doses (55, 175, 550, 1,750, 2,000 mg/kg). Plethysmometer was used to measure the inflammation of the paw before and after treatment. The result shows diclofenac, a standard drug that reduces paw inflammation by 32–39%. Methanolic extract of *A. officinarum* significantly inhibits edema in rats (Honmore et al., 2016). Another study by Rajendiran et al. (2018) reported that *A. officinarum* plant extracts from dried plant roots using n-hexane were administered to male Wistar rats (150–200 g); induced with colitis by feeding with 5% of Dextran sulfate sodium (DSS) consecutively for five days resulted in a reduction in colon length and a significant increase in the relative colonic weight/length ratio in both acute and chronic groups compared to control animals. The rats were divided into different groups. One group is administered with standard sterile drinking water control. Another group is fed with 200 mg/kg of n-hexane extract of *A. officinarum* and analyzed for 18–20 days. Co-administration with *A. officinarum* extracts considerably decreased macroscopic injury in DSS provoked creatures and reduced the colon weight/length ratio. *A. officinarum* extracts alone did not affect the colonic weight/length ratio compared to control animals.

The anti-inflammatory action of *A. officinarum* (rhizome extract) at various concentrations (500, 750, and 1,000 µg/ml) revealed the highest restraint of hemolysis at 35.29% (500 µg/ml) and moderate hemolytic repression at 29.83% (1,000 µg/ml). In contrast, the membrane stabilization percentage ranged from 64.71% to 70.17% in a dose-dependent manner (Balamurugan et al., 2019). *A. officinarum* commonly possess a diarylheptanoid compound, 7-(4′-hydroxy-3′-methoxyphenyl)-1-phenylhept-4-en-3-one (HMP). Authors demonstrated the compound's anti-inflammatory properties on

PBMCs (human peripheral blood mononuclear cells) and RAW 264.7 (mouse macrophage cell line) *in vitro*. When RAW 264.7 cells were exposed against HMP (6.25–25 M), it significantly repressed LPS (lipopolysaccharide)-stimulated NO (nitric oxide) generation. HMP restrained the discharge of tumor necrosis factor-α (TNF-α) and LPS-provoked interleukin-1β (IL-1β, a pro-inflammatory cytokine) from human PBMCs (*in vitro*). Further, reverse transcription-PCR investigation and Western blotting confirmed that HMP attenuated LPS-provoked cyclooxygenase-2 (COX-2) protein expression, mRNA expression and inducible nitric oxide synthase (iNOS) in RAW 264.7 cells. Moreover, there is a reduction in nuclear factor-κB (NF-κB) DNA binding provoked by LPS in RAW 264.7 cells exposed to HMP treatment. It was also confirmed that in LPS-stimulated RAW 264.7 cells, phosphorylation of p44/42 MAPK was considerably repressed by HMP, but the activation of p38 MAPK was not changed. These outcomes inferred that there is suppression of LPS-provoked synthesis of IL-1β, TNF-α and NO, and expression of COX-2 and iNOS genes by inhibiting NF-κB induction and phosphorylation of p44/42 MAPK mediated by HMP treatment from the lesser galangal (Yadav et al., 2003).

79.3.3 ANTIPROLIFERATIVE ACTIVITY

Tumor is a worldwide disease that does not have a proper remedial measure. According to Ghil (2013), when *A. officinarum* extract was used against MCF-7 cell lines of breast cancer in humans using MTT assay, the multiplication of MCF-7 cell lines was significantly reduced, the mechanism behind is the plant extract does not allow the cancer cell lines to multiply, they suppress the cell cycle in S-phase. *A. officinarum* extract (100 μg/ml) is used against MCF-7 cell lines. They arrest the development of cycline, E2F1, and Cdk2, as these proteins are required for S-phase continuation signifying that *A. officinarum* has antiproliferative activity against MCF-7 cell lines. In a study by Omoregie et al. (2013), *A. officinarum* also has antiproliferative activity against acute monocytic leukemia. The results showed potent antiproliferative activity when the cancer cell lines were administered with chloroform, methanol, and dichloromethane (DCM) leaf extract of lesser galangal. ME showed 78 ± 10%; acetone showed 100 ± 35% of THP-1 cell mortality. *A. officinarum* extracts showed anticancer activity for several tumor cell lines, namely lung cancer, neck squamous carcinoma and hepatocellular carcinoma. It also arrests the mortality caused by neuroblastoma cell lines. The bioactive compounds in *A. officinarum* extract inhibit the death of healthier cells in human pancreatic cancer (Abubakar et al., 2018).

An et al. (2008) conducted a cytotoxicity biological assay on plant extracts obtained from *A. officinarum* analyzed for anticancer activity against different human cancer cell lines MCF-7, SF-268, and HepG2. Spectrochemical analysis proves the presence of four diarylheptanoids compounds viz, two diarylheptanoids (**1**, **2**), and two other known analogs (**3**, **4**) separated from the *A. officinarum* (rhizomes). The unique compounds interpreted by NMR studies were known to be (5*R*)-5-hydroxy-7-(3-methoxy-4, 5-dihydroxyphenyl)-1-phenyl-3-heptanone (**1**) and (5*S*)-5-hydroxy-7-(3, 4-dihydroxyphenyl)-1-phenyl-3-heptanone (**2**); the analogs identified were 7-(3,4-dihydroxyphenyl)-1-(4-hydroxy-3-methoxyphenyl)-4-en-3-heptanone (**3**) and (5R)-5-hydroxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-3-heptanone (**4**), and. These cancer cell lines were cultured, multiplied, and tested with the plant extracts with 0.1% DMSO as a vehicle. The outcome shows that 7-(3,4-dihydroxyphenyl)-1-(4-hydroxy-3-methoxyphenyl)-4-en-3-heptanone (**3**) showed moderately potent cell mortality towards these tumor cell lines when compared to remaining diarylheptanoids compounds.

Alpinia officinarum rhizomes were investigated for their anticancer activities *in vitro* against A-549 (lung carcinoma), (HCF-126) cervical carcinoma, PC3 (prostate cancer), and CACO (colorectal carcinoma). Evaluating the antitumor activities (*in vitro*) of the investigated plant rhizomes extracts conferred a potent cytotoxic influence on the development and growth of certain cell lines contrasted to the standard control vinblastine sulfate. The actions registered against cell lines; CACO (IC_{50}: 7.6 ± 0.3 μg/ml; CACO) and A-549 (IC_{50} 6.72 ± 0.5; lung carcinoma) comparatively better than standard control vinblastine sulfate recorded an IC_{50}: 30.3 ± 1.4 μg/ml (CACO cell lines) and IC_{50}: 24.6 ± 0.7 (A-549 cells). Furthermore, the impact of the *Alpinia officinarum* rhizome extract was also encouraging against three other cancer cell lines Hela (cervical), Pc3 (prostate), and HCT-116 (Colon). The most potent effect was recorded for Hela cells with an IC_{50} (24.5 ± 1.1 μg/ml) which was more potent than the standard drug, vinblastine sulfate (59.7 ± 2.1 μg/ml) (Alasmary et al., 2019).

79.3.4 ANTIBACTERIAL ACTIVITY

In a study, four already known diarylheptanoids from *Alpinia officinarum* (rhizomes) was isolated from the ME 5-hydroxy-1,7-diphenyl-3-heptanone (2), 1,7-diphenylhept-4-en-3-one (1), and 7-(4″-hydroxy-3″-methoxyphenyl)-1-phenyl heptan-3-one (4) and 5-hydroxy-7-(4″-

hydroxy-3″-methoxyphenyl)-1-phenyl-3-heptanone (3). 7-(4″-actetate-3″-methoxy phenyl)-1-phenyl heptan-3-one (5), was the acetate derivative of (compound 4). These five diarylheptanoid compounds displayed encouraging *ex vivo* and *in vitro* antitubercular activity upon latent *Mycobacterium tuberculosis* H37Ra, IC_{50} values ranging between 0.13–22.91 and 0.34–47.69 μM, sequentially. Each compound displayed relative action toward *Mycobacterium bovis* BCG (dormant phage). These compounds were moderately cytotoxic (300 micro-molar concentrations against three human cancer cell lines and A549, THP-1 and Panc-1 (Honmore et al., 2016)).

A study by Srividya et al. (2010) evaluated the antibacterial characteristics of *A. officinarum*. The hydroalcoholic extract and ME was tested for their bioactives. The presence of tannins, saponins, and flavonoids are confirmed. The total flavonol and phenol were 54.02 and 50.1 mg/g, respectively. *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, and *Pseudomonas aeruginosa* were examined. The hydroalcoholic extract of the plant with a concentration of 1,000 μg, 500 μg and 250 μg, exhibited 27, 23, and 18 mm and 38, 29, and 24 mm as the zone of inhibition for the gram-positive bacteria; *Bacillus cereus* and *Staphylococcus aureus,* respectively. The control (tetracycline) exhibited 25 and 35 mm as the zone of inhibition for *B. cereus* and *S. aureus,* respectively. In gram-negative bacteria *viz, P. aeruginosa* and *E. coli,* the hydroalcoholic plant extract with a dosage of 1,000 μg, 500 μg and 250 μg, exhibited 17, 15, and 14 mm; and 23, 18, and 13 mm as the zone of inhibition, respectively. The control (tetracycline) exhibited 19 and 20 mm as the zone of inhibition for *P. aeruginosa* and *E. coli,* respectively.

The rhizome extracts of *A. officinarum* exhibited antimicrobial activity against three gram-negative bacteria, *Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Escherichia coli,* two fungal cultures *Aspergillus flavus* and *Candida albicans* and three gram-positive bacteria *Enterobacter faecium, Streptococcus pyogenes, Staphylococcus aureus.* Tetracycline is used as a standard control. *Alpinia officinarum* displayed restraint towards all the microbes examined. The maximum zone of inhibition was toward *E. faecium* and *K. pneumoniae* (27 mm), and the fungi *A. flavus* with 34 mm (Balamurugan et al., 2019).

Butanol and MEs of *A. officinarum* were assessed for their antibacterial activity. Seven bacterial cultures, *Micrococcus roseus, Bacillus subtilis, Staphylococcus aureus, Shigella dysenteriae, Klebsiella pneumoniae, Pseudomonas fluorescens,* and *Escherichia coli*, were chosen for the study. Butanol and MEs of *A. officinarum* were administered. The result confirms

that *A. officinarum* plant extracts show a more significant zone of inhibition for bacterial culture in the range of 10–24 mm for methanol and 10–22 mm for butanol extracts, respectively (Aly and Gumgumjee, 2011). In a study, *Bacillus subtilis*, *Pseudomonas fluorescens*, *Escherichia coli*, and *Xanthomonas* sps were tested upon hydro extracts of *A. officinarum* revealed that they have excellent inhibition for *E. coli*, and EE shows good inhibition for remaining bacterial cultures, the inhibition zone ranges from 16–26 mm (Naing et al., 2019).

79.3.5 ANTI-VIRAL AND ANTI-FUNGAL ACTIVITY

Various studies on phytochemical constituents of *A. officinarum* showed antiviral activity. The plant extracts and acyclovir show inhibition of the herpes simplex virus (HSV-1). *A. officinarum* extract of 250 mg/kg and acyclovir show that the survival time of mice affected with virus increased and reduced the damage caused by the virus in affected mice. This plant extract also shows potent activity against influenza caused by the H1N1 virus (Abubakar et al., 2018). A study by Konno et al. (2011) shows that *A. officinarum* exhibits antiviral activity on polio, measles, and respiratory synthetical virus (RSV). In another study to examine the antiviral activity of *A. officinarum*, female BALB mice (20–22 g) of 42 days old were taken for study and the animals were injected with the virus causing plague, and plant extract of dosage (30 and 100 mg/kg) was administered three times a day; another rat group with oseltamivir as a standard drug and one group with vehicle control. The final result showed that the control group faced a severe loss of body weight and led to death, but the rat groups administered with standard drug and plant extracts inhibited the loss of body weight and increased the life of rats (Sawamura et al., 2010). Antifungal activity was examined for *A. officinarum*, against fungal cultures of *Aspergillus niger*, *Candida albicans, Alternaria solani*, and *Fusarium oxysporum,* which showed a sizeable inhibitory zone against these fungi, representing that *A. officinarum* has potent antifungal activity (Aly and Gumgumjee, 2011).

79.3.6 ANTI-ARTHRITIC ACTIVITY

Arthritis is one of the deadly diseases affecting the joints of bones and leads to the enlargement of bone joints. Anti-arthritic activity of the EE of *A. officinarum* was evaluated. Male Sprague Dawley rats of weight 160–180

g was chosen as animal models. The animals were induced with arthritis by injecting Freund's adjuvant (0.1%), the volume of swelling in joints of rats was measured. Another set of rats were treated with prednisolone (10 mg/kg) acts as a standard. The remaining sets of rats were treated with *A. officinarum* plant extract with various dosages. This plant extract of 500 mg/kg shows promising effects on arthritis (Lee et al., 2009). According to Abubakar et al. (2018), the plant extract of *A. officinarum* is used for the treatment of osteoporosis, where the minerals in bones get reduced periodically and lead to weaker bones, 300 mg/kg of *A. officinarum* extract prevents the reduction of bone minerals and enriches minerals in the bones.

Bovine serum protein denaturation (BSPD) and egg albumin denaturation techniques (EAD) were done to examine the anti-arthritic action of the *A. officinarum* at various concentrations viz, 100, 200, 300, 400, and 500 µg/ml of rhizome extract. The anti-arthritic action ranged from 57.88% to 77.62% in a dose-dependent manner. The activity range of diclofenac sodium as a standard was from 59.31 to 73.44% in the BSPD method. In the EAD method, the activity range was observed from 21% to 37.58% in a dose-dependent manner, with the standard drug diclofenac sodium exhibiting values ranging from 12.2 to 26% (Balamurugan et al., 2019).

79.3.7 ANTIOBESITY ACTIVITY

Obesity is a major problem throughout the world which paved the way for several diseases and disorders like hypertension, diabetes mellitus (DM), cardiac disease, and hyperlipidemia. It affects all the people in the world without any gender difference. The plant *A. officinarum* rhizome roots were dried and made into an extract. Female Wistar rats of weight 155–220 g was taken into the study. Rats were administered with two different diets, one with a standard diet (SD) and another with a high-fat sugar salt diet (HFSSD) for more than one month. Before treating the animals with plant extracts, the body weight, blood pressure, and lipid content were analyzed. Then the HSSD rats were treated with *A. officinarum*, and the result showed a decrease in body weight, blood pressure, and lipid contents (Javaid et al., 2021). Another experiment was summarized to prove the antiobesity activity of *A. officinarum*. In this study, the phenolic contents of *A. officinarum* are obtained and administered for male Sprague Dawley rats (45–55 g). The rats were separated into four groups, administered with normal and high-fat diets, treated with *A. officinarum* extracts. The result revealed that *A.*

officinarum reduces the body weight, lipid, and serum levels than the normal control animals (Xia et al., 2010).

79.3.8 EFFECT ON REPRODUCTIVE HORMONES AND ORGANS

Impotence is a severe problem of present generations due to several factors; the chemical drug is ineffective with side effects. The solution is to go with plant-based drugs in different forms. Male albino Sprague Dawley rats of 220–250 g was taken as an animal model in a study, and they were injected with lead acetate, which reduces the fertility of rats periodically. They were treated with *A. officinarum* at various dosage levels 5%, 7.5%, and 10%, respectively, for two months; after the completion of the experiment, the rats were sacrificed and analyzed for the sperm level. *A. officinarum* increases sperm count and motility (Negm and Ragheb, 2010). In a study by Bebars et al. (2021), albino rats (200–250 g) were administered with N-hexane extracts of *A. officinarum* rhizomes. The rats were separated into five groups, a control; two groups treated with *A. officinarum* extract alone, the third group is administered with sotalol control, four, and five with sotalol and *A. officinarum* extract with different combinations; results indicate that the sotalol group showed a drop in sperm count, total testosterone level and serum SOD level but in AO extracts showed an increase in all these levels which depicts the positive effects on male reproductive hormones and organs.

79.3.9 ANTI-ULCER ACTIVITY

In a study, female Wistar rats of weight 18–22 g was taken as animal models. One group was administered carboxymethyl cellulose as a positive control; another group received ranitidine, a standard drug. DPH, a bioactive compound present in *A. officinarum was* given to the treatment groups for seven days orally. After the experiment, the groups were analyzed for ulcer index. The result shows positive effects by reducing ulcer index levels (Lin et al., 2015). Sprague Dawley rats (200–230 g) as an animal model with male and female rats were taken for the study. One group was a vehicle, and another group was a model group. The rats were equally divided into subgroups; one was fed with bismuth potassium citrate and another with AO extract. The rats were induced with gastric ulcers by administering indomethacin, and the rats were sacrificed after the experiment. Finally, the

gastric ulcer index (GUI) was analyzed. The report shows that AO extracts reduced the GUI values from 22 to 2%, depicting *A. officinarum* as good medicine for treating ulcers (Gong et al., 2018).

79.3.10 A. OFFICINARUM AGAINST ALZHEIMER'S DISEASE

One of the deadly neurogenerative disorders is Alzheimer's disease which is prevalent in aged people and leading to death. They usually suffer from memory loss due to Alzheimer's disease, which causes acetylcholinesterase (AChE) to affect neurons, the foremost reason for memory loss. *A. officinarum* extract inhibits the AChE responsible for the occurrence of the disease. Amyloid-β (Aβ) is the primary cause of Alzheimer's disease. It releases more than 40 amino acids that affect the neurons and neurotransmitters present in the brain and stagnates at the synapse. The hydro extract of *A. officinarum* shows promising results against Alzheimer's disease (Mukherjee et al., 2021).

79.3.11 ANTIDIABETIC ACTIVITY

DM is a global threat where more people are affected without any age and gender difference. Diabetes leads to several diseases like cardiac disease, obesity, and also damages the male reproductive organs. In this experiment, male Wistar albino rats (180–250 g) of 8 weeks old were induced with diabetes by injecting streptozotocin (STZ). The rats were segregated into different groups; one as non-diabetic with the administration of normal saline, another group as diabetic control with the administration of normal saline, and the remaining groups administered with *A. officinarum* extracts of 200 and 500 mg/kg dosage. The result showed an increase in sperm count, motility, and decreased blood glucose levels. Thus the *A. officinarum* extracts have dual benefits for DM and reproductive ability (Heidari et al., 2021).

79.3.12 PLATELET-ACTIVATING FACTOR (PAF)

To recognize efficient and unique PAF (platelet-activating factor) antagonists from the extracts of *A. officinarum;* fractionation and bioassay-controlled separation resulted in two new compounds;

6-(2-hydroxy-phenyl)-4-methoxy-2-pyrone (1) and 6-hydroxy-1,7-diphenyl-4-en-3-heptanone (4) and three already recognized diarylheptanoids *viz,* apigenin (5), 1,7-diphenyl-5-methoxy-3-heptanone (2), and 1,7-diphenyl-4-en-3-heptanone (3). The diarylheptanoids 1, 2, and 3 displayed powerful PAF receptor binding repressor actions with an IC_{50} of 1.3, 5.0, and 1.6 lM, sequentially. the results thus confirm that diarylheptanoids from *A. officinarum* are a new source of powerful PAF antagonists (Fan et al., 2007).

79.3.13 MELANOGENESIS INHIBITORY ACTIVITY

The hydro acetone rhizome extract of *Alpinia officinarum*, extracted with 80% aqueous acetone, inhibited melanogenesis in murine B16 melanoma 4A5 cells (theophylline-stimulated). Four diarylheptanoids isolated from the extract *viz,* [7-(400-hydroxy-300-methoxyphenyl)-1-phenylhept-4-en-3-one, 5-hydroxy-1,7-diphenyl-3-heptanone, 3,5-dihydroxy-1,7-diphenylheptane and 5-hydroxy-7-(400-hydroxy-300-methoxyphenyl)-1-phenyl-3-heptanone] along with two flavonols (galangin and kaempferide) repressed melanogenesis. In addition, the flavanoids and 7-(400-hydroxy-300-methoxyphenyl)-1-phenylhept-4-en-3-one repressed mRNA expression of tyrosinase-related proteins-1 and 2, and tyrosinase levels of microphthalmia linked transcription factors (Matsuda et al., 2009).

Tyrosinase inhibition, UV absorption, and melanin biosynthesis, and whitening effects were investigated in the flavonoid constituents of *Alpinia officinarum* against B16 mouse melanoma cells; The melanin content was reduced to 1.161 mg/105 cell for galangin and 1.276 mg/105 cell for flavonoid mixture. The melanin control was 1.632 mg/105 cells. Both galangin and flavonoid compounds decreased melanin generation with repression of 28.86% and 21.81% at a concentration of 29 mg/mL and 26.5 mg/mL (107.4 mM), respectively. Tyrosinase repression by the flavonoid compounds and galangin increased with a decrease in concentration. At more moderate concentrations, galangin exhibited antagonistic repression (21.23 mg/mL). Moreover, galangin and flavonoid mixture showed a broad absorption band associated with the UV-B area at 270, 290 nm. These observations suggest that galangin may be a whitening factor and a hopeful source for skin melanoma prevention (Lu et al., 2007).

KEYWORDS

- ***Alpinia officinarum***
- **lesser galangal**
- **terpenoids**
- **interleukin-1β**
- **nuclear Factor-Kb**
- **alzheimers disease**
- **tumor necrosis factor-α**

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CHAPTER 80

Medicinal Properties and Pharmacological Effectiveness of *Aspalathus linearis* (Burm. f.) R. Dahlgren

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80.1 INTRODUCTION

Aspalathus linearis (Burm. f.) R. Dahlgren (Fabaceae) has been identified as a well-recognized herbal tea, rooibos. This is a well-marked herbal product in numerous parts of the globe, in more than 37 countries, including the United States of America, Germany, the United Kingdom, and the Netherlands, which constituted 86% of the export market in 2010. The plant has a low tannin status and is caffeine-free, as well as possesses diverse potential health-promoting features such as antioxidant activity and many others (Joubert and de Beer, 2011).

Also, the health and biological action of this plant have been reported because of their bioavailability, bioactivity, and potential herb–drug interactions (Rampedi and Olivier, 2008; Joubert et al., 2008, 2009; Marnewick, 2009; McKay and Blumberg, 2007; Joubert and Schulz, 2006). Several scientists have reported the economic importance of *Aspalathus linearis* in the production of different beverage drinks and its tremendous economics value to global beverage industry capable of generating huge amount of

income thereby changing the global landscape of bioeconomy. Interestingly, the application of different technologies in the conversion of rooibos has a medicinal herbal tea into value-added products has contributed significantly to cosmetic markets, beverage, nutraceutical, drugs, and food industries (Joubert and Schulz, 2006; Huang et al., 2008; Chuarienthong et al., 2010; Glynn, 2010; Joppe et al., 2009).

80.2 BIOACTIVE CONSTITUENTS

The following bioactive constituents are present in the *Aspalathus linearis* such as polyphenols, tannins, bisfisetinidol-(4β,6:4β,8)-catechin, procyanindin B3, aspalathin, aspalalinin, flavones like orientin, vitexin, isoorientin, isovitexin, luteolin, chrysoeriol, and flavanones like dihydro-orientin, dihydro-isoorientin, and hemiphlorin, and flavonols like quercetin, isoquercitrin, hyperoside, and rutin (Lieberei et al., 2007).

80.3 PHARMACOLOGY

Aspalathus linearis has been reported to contain many bioactive molecules and secondary metabolites with several health benefits such as antioxidant, hypoglycemic, antispasmodic, antiallergic, photoprotective, estrogenic, anti-inflammatory, and anti-pyretic activity (Fukasawa et al., 2009; Ajuwon et al., 2014).

80.3.1 CARDIOVASCULAR EFFECTS

Joubert and de Beer (2011) reported that *Aspalathus linearis* contains unique polyphenols tannins, bisfisetinidol-(4β,6:4β,8)-catechin, procyanindin B3, aspalathin, aspalalinin, flavones like orientin, vitexin, isoorientin, isovitexin, luteolin, chrysoeriol, and flavanones like dihydro-orientin, dihydro-isoorientin, and hemiphlorin, and flavonols like quercetin, isoquercitrin, hyperoside, and rutin. These bioactive molecules are known with anti-inflammatory, hypoglycemic, hypolipidemic, and chemoprotective functions.

Maarman (2019) revealed that natural active biomolecules derived from *Aspalathus linearis* are very potent for cardioprotective interventions such as myocardial ischemic injury and diabetic cardiomyopathy. The author reported that the mechanisms of its cardioprotective activity involves preservation

and maintenance of cardiac energy homeostasis through the activation of the AMPK-GLUT-4 glucose oxidation pathway, reduction in reactive oxygen species (ROS), increase in ATP production and mitochondrial activity in the muscle.

Other contributory mechanisms are reduction in apoptosis signaling, cardiolipin, and G-protein-coupled receptor kinase-2, mitochondrial connexin-43. Erlwanger and Ibrahim (2017) reported that *Aspalathus linearis* possesses Aspalathin, a known antioxidant, cardioprotective, antidiabetic, antihypertensive, antimutagenic agent. The authors also stated that there are other polyphenolic compounds like isoorientin, chryoseriol, orientin, isovitexin, rutin, nothofagin, hyperoside, quercetin-3-O-robinobioside, enolic phenylpyruvic acid-2-O-β-d-glucoside, and isoquercetin with antioxidant, hypoglycemic, antiobesity effects. The proposed mechanism of the cardioprotective function is through regulating the expression of the glitazone receptor peroxisome proliferator-activated receptor (PPAR) gamma, anti-inflammation through the Jak2 signaling and proinflammatory IL-6 cytokine pathway, increased expression of Bcl2, increased production of NO. Dludla et al. (2014) revealed that *Aspalathus linearis* contribute to cardioprotective activity when consumed by individual due to a large number of bioactive molecules acting as anti-inflammatory and antioxidants in cardiomyocytes.

In 2018, Johnson et al. showed that Aspalathin derived from *Aspalathus linearis* is a C-glucosyl dihydrochalcone having potent antioxidant property. This bioactive molecule can be utilized for the treatment of metabolic disorders linked with oxidative stress like type 2 diabetes, obesity, and cardiovascular. Aspalathin or aspalathin-rich rooibos extracts are of great nutraceutical benefit such as improving lipid and glucose metabolism and adjunctive therapy. Studies have shown that antioxidant transcription factors like Nrf2 linked with downstream proteins and genes like glutathione (GSH) have appeared as an important target in the suppression of oxidative stress-induced cardiometabolic dysfunctions. Generally, the pathophysiology of cardiometabolic dysfunctions involves several risk factors like increased fasting blood glucose, increased serum triglycerides, and increased blood pressure, resulting in the development of cardiovascular complications. Studies have also revealed that these bioactive molecules in *Aspalathus linearis* can effectively regulate protein kinases like JNK, ERKs, IKK, AMPK, leading to reduced inflammatory and cellular damage.

In recent times, attention has been shifted to the beneficial role of aspalathin derived from *Aspalathus linearis* as an antioxidant, anti-inflammatory signaling molecules in lipid and carbohydrate regulation. These polyphenols

possess huge capability to ameliorate cardio metabolic syndrome through activation and stimulation of insulin secretion, enhancing glucose tolerance, inhibition of α-amylase and α-glucosidase enzyme function, enhancing uptake of glucose in the skeletal muscle and pancreas, suppressing NF-Kb and PKC while stimulating the AMPK activity. Generally, aspalathin stimulate the expression of CPT1, thus increasing the fatty acids oxidation process in muscle under the regulation of important lipid metabolic genes, like ACC, SCD1, FAS responsible for insulin resistance (IR) development in heart tissue, liver, fat, and muscle (Mazibuko-Mbeje et al., 2019).

Aspalathin stimulate AMPK and decrease hepatic enzyme expression and transcriptional regulators like SREBP-1/2, ChREBP, and PPARγ linked with either lipogenesis or gluconeogenesis. Ajuwon et al. (2014) also reported that beneficial role of aqueous *Aspalathus linearis* extract in suppressing the liver injury induced by LPS through inhibition of pro-inflammatory cytokines generation and oxidative stress. Dludla et al. (2017) reported that diabetes is seriously linked with cardiovascular disorders due to chronic hyperglycemia which alters mitochondrial physiology, dysfunctional NADPH oxidase enzyme, increased myocardial injury. The authors reported that plant-based diets like *Aspalathus linearis* can modulate the intracellular signaling pathways, enhances the expression of nuclear factor (erythroid-derived 2)-like 2 (Smit and Swart, 2018).

80.3.2 NERVOUS SYSTEM EFFECTS

Aspalathus linearis has been reported to contain polyphenolic compounds with cardiovascular and neuroprotective functions. This plant has been evaluated for the neurobehavioral effects in bisphenol A induced central nervous system (CNS) degeneration. The plant was able to protect the brain functions by increasing the antioxidant activity of the cerebral or cerebellar, increase the length of hippocampal CA1, decrease the accumulation of lipid peroxides, restores the cells of cerebellar Purkinje, decrease level of steroidal hormone and astrocyte function. Thus, it was suggested that *Aspalathus linearis* offers a strong neuroprotective effect against functional, biochemical, and structural changes in the CNS induced by BPA. This neuroprotective ability has been connected with the presence of high number of polyphenols like nothofagin, flavones (iso-orientin, orientin, luteolin-7-O-glucoside, vitexin, chrysoeriol, isovitexin, and luteolin), flavanones (hemiphlorin, dihydro-iso-orientin, and dihydro-orientin), flavonols (quercetin hyperoside, rutin,

quercetin-3-robinobioside, and isoquercitrin), phenolic acids, esculetin, lignans, orientin, aglycones, iso-orientin luteolin, and chrysoeriol (Joubert et al., 2004).

Hong et al. (2014) documented the functions of *Aspalathus linearis* in the treatment of diverse neurodegenerative disorders like Alzheimer's disease, frontoparietal dementia due to presence of a large number of polyphenolic compounds like ellagic acid, flavanones, flavonoid, proanthocyanidins, triterpenes, and saponins. Over the last few decades, serious attention has been given to the beneficial role of many polyphenolic compounds present in plants such as *Aspalathus linearis* for the physiological regulation of many biological functions. The antioxidant and chemopreventive mechanisms of *Aspalathus linearis* has provided much knowledge about the biological role of these bioactive compounds in the CNS.

Snijman et al. (2007) revealed that *Aspalathus linearis* consist of isovitexin, aspalathin, vitexin, isoorientin, isoquercitrin, orientin, hyperoside, rutin, quercetin, chrysoeryol, luteolin capable of acting pharmacologically as biomolecules in the suppression of nervous tension in the body. Pyrzanowska et al. (2019) reported that *Aspalathus linearis* showed significant progress in long term spatial memory. 3-methoxytyramine and striatal dopamine measurement were equally elevated in the treated group.

Also, Akinrinmade et al. (2017) revealed that fermented Rooibos herbal tea suppressed the brain tumor/edema formation and neuronal apoptosis induction. Hong et al. (2014) reported the antioxidant role of *Aspalathus linearis* in preventing neurodegenerative responses due to brain oxidative stress. The plant offered a neuronal protection by preventing lipid peroxidation (LPO), restored stress-induced protein degradation, reverse the elevated stress-linked metabolites like FFA and 5-HIAA, control GSH metabolism and regulate alterations in the activities of endogenous antioxidant enzymes.

80.3.3 ANTICANCER EFFECTS

Rooibos, *Aspalathus linearis* is a rich source of polyphenols such as aspalathin, vitexin, rutin, and luteolin. Additionally, it was also reported to contain nothofagin and chrysoeriol, known for their antioxidative effects (Herbst, 2015). These polyphenols are the basis of the health boosting effects of *A. linearis*, which includes suppression of inflammation, anti-mutagenic, antioxidative, and anti-tumor effects.

Mutation is the basis of carcinogenesis. The anti-mutagenic mechanisms of *A. linearis* could be via direct inactivation of mutagens, prevention of biochemical activation of mutagens, modulation of DNA repair and replication, protection of DNA from mutagens and modulation of detoxification by the liver (Słoczynska et al., 2014).

In a study, the ME had a higher concentration of these polyphenols than the aqueous extract. Pre-malignant cells were discerningly targeted by the ME by a mechanism involving suppression of cell proliferation at a lower concentration and stimulation of apoptosis at an elevated concentration (Magcwebeba et al., 2016b). Tsuneoka et al. (2009) documented the ability of *A. linearis* to disrupt mitochondrial function resulting in lower production of ATP has deleterious effect on cancer cells by arresting cell cycle and inducing cell death. In another report, the pro-apoptotic effect of *A. linearis* was via the inhibition of Bcl-2 proteins (Yadav et al., 2013). The ability of *A. linearis* to suppress the induction of chromosomal aberrations as well as inhibit age-dependent assemblage of lipid peroxides was reported (Kunishiro et al., 2001). Kunishiro et al. (2001) further observed the immune stimulation potentials of *A. linearis*. This was via antigen-specific antibody production by activating macrophages, induction of transition of Th2 to Th1. This further supports its anti-tumor effects.

The inflammation suppressive effect of *Aspalathus linearis* could relate to the availability of aspalathin. Aspalathin suppressed inflammation via the inhibition of Toll-like receptor 4 in lipopolysaccharide (LPS)-treated human umbilical vein endothelial cells (HUVECs). It also enhanced antioxidant effects while inhibiting pro-oxidants' generation and LPO in H9c2 cardio myoblasts (Shabalala et al., 2020). It also modulates genes responsible for lipid and carbohydrate metabolism. *A. linearis* also inhibited COX-2, a mediator of inflammation (Mahomoodally, 2013).

Chrysoeriol is a methylated metabolite of luteolin with reported antioxidant ability (Zeng et al., 2016). In a study, chrysoeriol reduced the production of ROS as well as selectively destroyed leukemic cells. Furthermore, it enhanced activated T-Cells (NFAT) nuclear factor (Kim et al., 2010). Also, chrysoeriol also induced lung cancer cell death via mechanisms involving suppression of the MAPK/ERK signaling route, and induction of autophagy. Autophagy-linked proteins including LC3-II and Beclin-1 were elevated while the expression of p62 level was reduced (Wei et al., 2019).

Takemura et al. (2010) reported that chrysoeriol inhibited CYP1B1 which catalyzes the hydrolysis of 17-β-estradiol to a carcinogenic product, 4 hydroxy 17-β-estradiol. In another study, it regulated the activity of BCRP

which plays a key function in multidrug resistance (MDR) (Tan et al., 2013). Lai et al. (2018) reported that chrysoeriol inhibited c-Met and vascular endothelial growth factor 2 (VEGF2), hence inhibiting tumor progression and drug resistance. Furthermore, the binding of 8-chrysoeriol to BH3 domain of Bcl2 proteins induced apoptosis. Bcl2 proteins are over-expressed in cancer cells (Barreca et al., 2020).

80.3.4 ANTIULCER EFFECTS

The anti-ulcer potential of rutin, a flavonoid present in *A. linearis* has been reported (Serafim et al., 2020). Rutin inhibited gastric mucosal ulceration in laboratory animals (Barnaulov et al., 1983). The plausible gastric-protective mechanisms of rutin include activation of endogenous platelet-activating factor (PAF) and reduction of lipoperoxides and upregulation of GSH peroxidase (Mota et al., 2009). Rutin also inhibited proton pump activity in another study (Dubey et al., 2013). Furthermore, reduced MDA levels were reported upon the administration of rutin to lab animals in another study (Olaleye and Akinmoladun, 2013).

The antiulcerogenic effect of *A. linearis* could also be attributed to the antibacterial potentials of its flavonoids such as vitexin, rutin, and luteolin (Adamczak et al., 2020). These flavonoids inhibit *H. pylori* infection.

80.3.5 IMMUNE-MODULATING AND ANTIOXIDATIVE EFFECT

Ajuwon et al. (2015) studied immune modulating, antioxidative, chemotherapeutic along with chemo-preventive actions of *Aspalathus linearis*, which have also been reported in other studies. They made available comprehensive information on the existing knowledge of the chemotherapeutic and biological activity of *A. linearis* along with its main flavonoids. In recent *in vivo* and *in vitro* (human and animal) investigation carried out with exceptional care paid to scientific circumstances where oxidative stress has been involved.

Also, Marnewick (2014) established the potential of *in vitro* antioxidant. A variation of oxidative damage/stress through extracts of *A. linearis* in animal experiment has also been reported. Recently, researchers have observed the bioactivity of *A. linearis* in humans. Collectively, several of these features is attributed to the acceptance of this medicinal tea which has been used as a health beverage, both internationally and locally.

In recent investigation, Xin et al. (2020) carried out a study on *in vivo* and *in vitro* using antioxidative, antidiabetic, and phytochemicals activities of *Aspalathus linearis* (rooibos tea). The concentrated extract of the study plant showed greatly *in vitro* through significant free radical scavenging activities. The studied plants have considerably introverted intestinal glucose intake along with a-amylase activities where there is an increase in muscle glucose uptake. On the profiling of phytochemical study which revealed the presence of coumestrol, quinolinic acid, 8-hydroxyquercetagetin, phloroglucinol, ajoene as well as umbelliferon were identified in *A. linearis*.

80.3.6 ANTIDIABETIC AND HEPATOPROTECTIVE EFFECTS

Aspalathus linearis (Rooibos) has been shown to exhibit hypoglycemic, hypolipidemic, and hepatoprotective effects. *In vitro* and *in vivo* studies regarding the effect of rooibos tea component at 1–100 micromolar in concentrations revealed a dose-related elevation in glucose absorption by L6 myotubes (Ulicna et al., 2003; Millar et al., 2020).

Kawano et al. (2009) documented that 0.1–0.2%, intake of Aspalathus in food was also shown to depress elevated fasting blood glucose in genetically mutated mice (db/db mice). The work of Najafian et al. (2016) indicated that asphalathin, an important constituent of the *Aspalathus linearis* as an alpha-amylase inhibitor, suppressed blood glucose in a dose-related mode and decreased elevated levels of LDL-c and TC but increased the level of HDL-c in streptozotozin-induced experimental rats. Green Rooibos and aspalathin depressed high fasting blood glucose following starch, maltose, and glucose intake via alpha-glucosidase and alpha-amylase suppression (Mikami et al., 2015).

Kawano et al. (2009) in their investigation reported that green rooibos extract boosted cellular glucose uptake in insulin-deprived condition by facilitating increased phosphorylation of 5^{i} adenosine monophosphate-activated kinase (AMPK) in L6 myotube model. In addition, Son et al. (2013) documented that asphalathin also accelerated 5^{i} AMPK, GLUT-4 transfer to cell membrane with uptake of cellular glucose by L6 myotubes.

Ulicna et al. (2003) studied the protective effect of rooibos tea in CCl_4 initiated hepatic injury in rats. They discovered that the extract exerted a curative effect evidenced by regression of hepatic fat accumulation and liver cirrhosis. Depression in elevated serum values of bilirubin, alkaline phosphatase (ALP), aspartate transaminase and alanine transaminase were

also noted. This suggests the potential of the plant in liver dysfunction management.

Interestingly, *Aspalathus linearis* was demonstrated to offer protection for the hepatocytes by ameliorating the damaging effects of carbon tetrachloride on the hepatocytes through the preservation of the hepatocyte's mitochondrial activity and ATP generation. Ajuwon and coworkers have also reported the liver protecting action of *Aspalathus linearis* in LPS-induced hepatic dysfunction. *A. linearis* extract mediates its liver protective effects through its anti-inflammatory and antioxidant-dependent mechanisms (Ajuwon et al., 2014).

80.3.7 EFFECT ON MALE REPRODUCTIVE FUNCTION

Most male reproductive dysfunctions have oxidative stress as part of the central modulating mechanisms. The antioxidative effect of *Aspalathus linearis* has been previously established by various investigators. The ROS-suppressing and free radical scavenging effects of *A. linearis* has been reported in various cells like the cardiac cells, skin cells, and osteoblastic cells (Dludla et al., 2014; Nash and Ward, 2016; Magcwebeba et al., 2016a). Furthermore, Awoniyi and colleagues revealed in their study that *Aspalathus linearis* extract exhibited oxidative stress-lowering effect in tissues of the testes of oxidative stress-induced rats through the increase activity of superoxide dismutase (SOD) and reduction in LPO. Hence, *A. linearis* extract will improve testicular health thereby enhancing male reproductive function via its antioxidant effect (Awoniyi et al., 2011). In addition, *A. linearis* increased percentage of motile sperm, sperm viability and sperm concentration in rats with oxidative testicular dysfunction suggesting beneficial effect of *A. linearis* on sperm quality as well as its function resulting enhanced male reproductive efficiency (Awoniyi et al., 2012; Opuwari and Monsees, 2014).

Ros-Santaella and Pintus (2017) documented sperm function enhancing the capacity of *A. linearis* extract using an *in vitro* experimental method. This study revealed that *A. linearis* increases sperm motility, preserves the integrity of the sperm membrane, and keeps the acrosome structure of the boar semen for about 96 hours in the liquid-storage medium (Ros-Santaella and Pintus, 2017). Therefore, *A. linearis* represents a natural means of enhancing and protecting sperm function and quality, majorly through antioxidant-dependent mechanisms.

KEYWORDS

- ***Aspalathus linearis***
- **cardiovascular effects**
- **Rooibos**
- **aspalathin**
- **platelet-activating factor**
- **vascular endothelial growth factor**

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CHAPTER 81

Medicinal and Pharmacological Attributes of *Acalypha hispida* Burm. f.

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81.1 INTRODUCTION

Acalypha hispida Burm. f. (Euphorbiaceae) has been described as a plant that has sparsely branched shrub and with an erected position. The plant normally serves as a decorative plant most especially in houses and in the garden. It originates from the Oceania, but it's commonly found in the tropics of Africa, America, and Asia (Onocha et al., 2010). Studies have shown that *A.*

hispida can be used as flower decoction for the treatment of kidney ailment and as a diuretic. Many parts of the *A. hispida* have been tested for their medicinal purposes. The leaf poultice is said to be useful for the treatment of leprosy, while the internal decoction of the leaf also helps in the management of gonorrhea and can also be used as a laxative. The bark had been applied for the treatment of asthma and cough (Onocha et al., 2010). The leaves possess diuretics and laxative properties which are explored for the management of gonorrhea and leprosy diseases. Moreover, some other section of the plant is utilized for the treatment of pulmonary-related diseases, infectious diarrhea, and as cough medicine in the management of asthma (Seebaluck et al., 2015).

81.2 BIOACTIVES

Girish and Vaidya (2018) reported that *Acalypha* species possesses phytochemical constituents like saponins, alkaloid, tannins, phlobatanins, phenolics, sesquiterpenes, cardiac glycosides, monoterpenes, polyphenols, triterpenoids, gallic acid, geraniin, corilagin, quercetin 3-O-rutinoside, anthraquinone, kaempferol 3-O-rutinoside with strong antihypertensive properties. Other biomolecules with known cardioprotective functions include tannic acid, uzarigenin, oleanolic acid, neriodorein, karabin, oleandrose, neriodin, nerium F, nerium D, oleanolic acid, gitoxigenin, digitoxigenin, neriantin, adyresin, odoroside, ursolic acid, scopolin, oleandrin, scopoletin, 16-acetyl gitoxigenin, oleandrigenin, dambonitol, and deacetyloleandrin. Several other studies have also reported the rennin-dependent anti-hypertension and cardiotonic activities of many of these biomolecules derived from *Acalypha* species. Again, Onocha et al. (2011) reported the anti-arrhythmic and anti-cholesterol activity of this plant attributing the effects to the presence of many phytochemical active constituents such as saponins, alkaloid, tannins, phlobatanins, phenolics, sesquiterpenes, cardiac glycosides, monoterpenes, polyphenols, triterpenoids. The cardiac glycosides and alkaloids from the plant can inhibit Na^+/K^+ enzyme pump which is responsible for the movement of sodium and potassium across any biological membrane.

Aboaba and Omotoso (2012) reported that the essential oil derived from the leaves of *Acalypha hispida* contains larvicidal activity. They revealed that the essential oils (EOs) contain sesquiterpenoids, nonanal, diterpenoids, 6,10,14, trimethyl-2-pentadecanone, geraniol, sesquiterpenoids, monoterpenoids, z-α-bisabolene, neral, and Oxygenated monoterpenoids which have

strong insecticidal and larvicidal properties. The leaf has been identified to contain phenolics, steroids, flavonoids, glycosides, saponin, and hydroxyanthraquinone (Okorondu et al., 2009). *Acalypha hispida* has been shown to contain palmitic acid, 6, 10, 14-trimethyl-2-pentadecanone, geranial, neral, triacontane, tetracosane, nonanal.

The phytochemical constituents available in *Acalypha hispida* are responsible for their diverse biological activities include steroids, saponin, reducing sugars, flavonoids, glycosides. Some of the biological active constitutes available includes cyanidin 3-*O*-β-galactopyranoside, cyanidin 3-*O*-(2″-galloyl-*β*-galactopyranoside), and cyanidin 3-*O*-(2″-galloyl-β-galactopyranoside), and acalyphidins M_1, M_2, and D_1 (Amakura et al., 1999; Reiersen et al., 2003; Bokshi et al., 2012). One of the phenolic compounds that is commonly seen in the extracts of *A. hispida* is Geraniin (Adesina et al., 2000). Geraniin is a hydrolysable tannin, a type of phenolic compounds common in this plant. Geraniin is said to be an effective antioxidant and antimicrobial agent (Adesina et al., 2000).

81.3 PHARMACOLOGICAL ACTIVITIES OF *ACALYPHA HISIPIDA*

Its antibacterial, antifungal, antiulcer, and antitumor properties have been reported in past studies (Onocha et al., 2011). Interestingly, the leaves possess some biological activities such as antifungal activities, antimicrobial, cytotoxic, antileprotic, but the flower part entails cytotoxic activity and DPPH free radical scavenging and anti-inflammatory**,** antioxidant activity (McLaughlin et al., 1999; Adesina et al., 2000; Ejechi and Souzey, 1999; Onocha et al., 2011).

81.3.1 ANTIOXIDANT ACTIVITY

Geraniin is said to be an effective antioxidant (Adesina et al., 2000). Geraniin does not give any unpalatable mouth reaction (Okuda et al., 1977). Geraniin has been shown to be a powerful antioxidant scavenging free radicals. The antioxidant activities of geraniin are said to better than many popularly known antioxidants like epigallocatechin gallate (EGCG), butylated hydroxytoluene (BHT), ascorbic acid and butylated hydroxyanisole (BHA) (Sudjaroen et al., 2012). Xanthine oxidase inhibitory activity of geraniin has also been demonstrated. Xanthine oxidase generates oxidative injury associated free radicals. Several other reasons have been suggested for the antioxidant's

property of geraniin; they include precipitation of proteins, inhibitory effect on lipid peroxidation (LPO), and enhancement of glutathione (GSH) level (Liu et al., 2016). The antioxidant activity of geraniin may also be improved by its ability to activate certain signaling pathways that ultimately result in the elevation of antioxidant enzymes (Adesina et al., 2000).

81.3.2 ANTIMICROBIAL ACTIVITY

The antimicrobial activities of *A. hispida* are due to some polyphenols and other compounds such as flavonoids, steroids, glycosides, saponin, and hydroxyanthraquinone in its extracts. Geraniin is known to be useful for the treatment of some microbial infections such as gonorrhea. The antimicrobial activities of geraniin have been classified to be bactericidal. The bactericidal effect of geraniin and other hydrolysable tannin may be associated with the disruption of liposomal membrane in bacteria (Cheng et al., 2017). Geraniin has also displayed several antiviral effects in an experimental assay. The antiviral activities of geraniin have been attributed to the inhibition of some essential enzymes in the virus. Enzymes such as proteases, integrase, and reverse transcriptase (RT) were shown to be inhibited by geraniin (Kakiuchi et al., 1985) while eliciting its antiviral activities. Geraniin can also bind to the CD4-gp120 thereby preventing the uptake of HIV (human immunodeficiency virus) and the multiplication of the virus in the MT4-T-lymphoid cells.

Another active ingredient from the *A. hispida* is corilagin. Corilagin has been tested in many bacteria for its antimicrobial activities Corillagin from *A. hispida* exhibited antimicrobial activities against some gram-negative bacteria and fungi. Adesina et al. (2000) showed that *A. hispida* inhibited *Candida pseudotropicalis*, *Staphylococcus aureus*, *Bacillus subtilis Pseudomonas aeruginosa*, and *Escherichia coli.* Li et al. (2013) demonstrated that Corilagin inhibited the growth of *Escherichia coli,* and *Candida albicans* by interfering with their membrane, but inhibited the growth in *Staphylococcus aureus* by binding to the Fib, SaeR, and SarS proteins. It usually binds protein type 7p on *Candida albicans* membrane.

The activities of gallic acid from *A. hispida* have not been fully ascertained and the available report seems to be strain specific. The analysis of the common ingredients found in *A. hispida* showed that the antimicrobial activities of *A. hispida* could be due to its interference with liposomal membrane, proteases, integrase, transcriptase, and the binding of its active

ingredient to $CD4^+$ cell. It can also mediate inhibition by binding to the Fib, SaeR, and SarS proteins in *S. aureus* and protein type 7p on *Candida albicans* membrane.

Decoction of the leaves and flowers of *Acalypha hispida* was administered as purgative and suitable in managing gonorrhea. The bark and the root of the plant are used in treating pulmonary complications. Decoction made from *A. hispida* and was used in managing dysentery caused by *Shigella dysenteriae.* Bokshi et al. (2012) also recounted potent antimicrobial effects on *Salmonella typhi, Escherichia coli, Shigella sonnei, Shigella boydii, Enterococcus faecalis, Streptococcus agalectiae, Staphylococcus saprophyticus, Shigella flexneri*, and *Streptococcus pyogenes* only at elevated concentration of the *A. hispida* ethanol extract. Osarumwense and Okunrobo (2013) reported that *Acalypha hispida* contain some active secondary metabolites such as Quercetagetin-7-arabinosyl-galactoside, glycosides, alkaloids, steroids, fatty oils, flavonoids, resins, tannins, mucilages, gums, calcium, and phosphorus responsible for its effectiveness as a medicinal plant. Gallic acid, geraniin, corilagin, kaempferol 3-O-rutinoside, and Quercetin 3-O-rutinoside were also found to be responsible for the antimicrobial efficacy of the plant (Adesina et al., 2000).

81.3.3 INSECTICIDAL AND MOSQUITO REPELLANT ACTIVITY

Onocha et al. (2011) revealed that bisabolane sesquiterpenes curcumene derived from *Acalypha hispida* act as insecticidal and mosquito repellant.

81.3.4 ANTIPARASITIC ACTIVITY

Okanla et al. (1990) reported the trypanocidal role of *Acalypha hispida* aqueous extract. In their study it was demonstrated that *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* induced trypanosome was ameliorated utilizing extract from the plant.

81.3.5 CARDIOVASCULAR EFFECTS

Shah et al. (2019) reported that many secondary metabolites derived from plant are very effective in providing cardioprotective function. Some of these bioactive molecules include diosgenin, sulforaphane, isoflavones,

carotinized, quercetin, and catechin, which have strong cardio protection property. Onocha et al. (2011) revealed that *Acalypha hispida* essential oil possess substantial phytochemicals with great pharmacological activity such as antioxidant, anti-inflammatory, and cardioprotective function. The authors revealed that the essential oil contains saponins, steroids, phlobatannins, flavonoids, phenolics, glycosides, and hydroxyanthraquinones. Others include terpenes, esters, ketones, bisabolane sesquiterpenes curcumene.

Alfarisi et al. (2020) demonstrated that *A. hispida* consists of ellagic acid, quercetin, phlobatin, gallic acid, saponin, hyroxylanetquinone, rutin, p-coumaric acid, catechins, flavones, kaempferol, flavonoids, myricetin, flavonols, phenolic acids, corilagin, and isoflavones with antioxidant and hypoglycemic activity.

81.3.6 NERVOUS EFFECTS

Medicinal plants like *Acalypha hispida* possess phytochemicals such as alkaloids, steroids, glycosides, flavonoids, resins, fatty oils, mucilage, gums, tannins, calcium, and phosphorus need to build the body and for nervous development and growth. Diet is known to provide energy sufficient for muscle and nervous development for instance, flavonoid have been demonstrated to have antiviral, antioxidant, and anti-inflammatory potentials (Iniaghe et al., 2009).

81.3.7 ANTIDIABETIC AND HEPATOPROTECTIVE EFFECTS

A study by Alfarisi et al. (2020) indicated that ethanol extract of the whole plant at 400 mg/kg body weight caused a glucose lowering effect. Around 96% ethanol extract at 300 mg/kg body weight dose was reported to exhibit a great hypoglycemic influence and this was due to a great inhibitory effect on alpha-glucosidase and alpha-amylase activities. Alfarisi et al. (2020) investigated the glucose lowering ability of *Acalypha hispida* in normal and diabetic rats. From their study, it was discovered that the extract caused a glucose suppressing effect by 300 mg/kg dose of extract which significantly suppress hyperglycemic index in the treated rats. They also observed that the extract remediated liver damage.

KEYWORDS

- ***Acalypha hispida***
- **antiparasitic activity**
- **antiulcer potential**
- **butylated hydroxytoluene**
- **hepatoprotective effects**
- **hyperglycemic**

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CHAPTER 82

Medicinal Properties of *Senna alata* (L.) Roxb. (Syn. *Cassia alata* L.) and Its Biological Activities

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82.1 INTRODUCTION

Senna alata (L.) Roxb. (Syn.: *Cassia alata* L.) is a plant that belongs to the family of Fabaceae. The plant has the capability to grow in the tropics. The plant flowers are bright yellow and have a fruit has a brown pod with brown seeds (Hennebelle et al., 2009). *Senna alata* has been applied in the treatment of numerous diseases, such as anti-inflammatory agent and treatment of wounds, management of diverse cure skin diseases and skin disorders, treatment of eczema, and antimicrobial agents while they could be applied in the reduction of headaches and paralysis and stomach pain during pregnancy. The presence of numerous phytochemicals such as steroids, terpenoids, alkaloids, flavonoids, saponins in *Senna alata* are responsible for their various biological activities (Sule et al., 2010; Akinmoladun, 2010).

82.2 BIOACTIVES

The biological effects of *Senna alata* could be attributed to the presence of a variety of bioactive compounds such as saponins, alkaloids, terpenoids, flavonoids, and steroids (Fatmawati et al., 2020). A previous study determined five anthraquinones; emodin, rhein, aloe-emodin, physcion, and chrysophanol in the root of *S. alata*. Furthermore, kaempferol, a flavonoid was also determined (Fernand et al., 2008). Other bioactive compounds including limonene, cinnamic acid, 1, 8-cineole, α-selinene, germacrene, β-caryophyllene, steroids, isoquinoline, volatile oils have been reportedly present in other parts of the plant (Oladeji et al., 2020).

Fatmawati et al. (2020) reported that *S. alata* possess flavones, flavonoids glycosides, flavonols, alanonal, β-sitosterol-β-D-glucoside, piperidine alkaloids, spectaline, cassine, 3-O-acetylspectaline and alatinon which are secondary metabolites extracted from the leaves, stems, flowers, and seeds utilized as therapeutic agents in diverse disease conditions. Olivier et al. (2017) demonstrated that *S. alata* contains quinones, tannins, anthraquinones, saponins, flavonoids, cardenolides, steroids, alkaloids, phenols, resins, and triterpenoids which are reported to be very strong antipyretic, analgesic, and antispasmodic effects.

Tatsimo et al. (2017) used methanol for the extraction of *S. alata* plant using hexane as the organic solvent. After separation and purification of the crude extract, the active compounds were identified using spectroscopic techniques. The three major metabolites obtained from ME of the plant were luteolin, 4, 5, 7-trihydroxy-2-methyl anthraquinone, aloeemodin, and kaempferol. Also, antibacterial activities of the leaf of *S. alata* might be linked to the presence of anthraquinone and flavonoid compounds.

Ranjanie et al. (2019) revealed the potency *S. alata* plant for their medicinal attributes as well as pharmacological activity. The seed, root as well as leaves are recognized for their therapeutic values. Some of the chemical compounds like naphthopyrone glycosides, anthraquinone glycosides, flavonoids, and phenolic compounds have been reported from this plant. The plant is normally used as herbal treatment against ringworm infection, leprosy, skin diseases, liver disorders and ophthalmic.

Oladeji et al. (2020) also reported importance of the *S. alata* plant for their medicinal attributes such as cure diabetes, typhoid, asthma, malaria, tinea infections, ringworms, blotch, scabies, eczema as well as herpes. Diverse portion of the plant have therapeutic substances that could be applied for the treatment of various infections and diseases. Numerous

biological compounds are present in the plant which are responsible for their antioxidant, antibacterial, dermatophytid, antifungal, hepatoprotective, anticancer, anticonvulsant, antilipogenic, antihyperlipidemic, antidiabetic, anthelmintic, antiviral as well as antimalarial activities. These biological activities might be linked to presence of these secondary metabolites such as alkaloids, tannins, terpenes, flavonoids, saponins, anthraquinone, cannabinoid alkaloids, phenolics, caryophyllene, 1,8-cineole, α-selinene, limonene, germacrene D, β-caryophyllene, pyrazol-5-ol, cinnamic acid, isoquinoline, methaqualone, reducing sugars, quinones, volatile oils along with steroids existing in diverse portion of the plant.

82.3 PHARMACOLOGY

Senna alata has been established to possess a very higher antifungal effectiveness, most especially those that could cause skin diseases and in the treatment of skin infected with ringworm (Reezal et al., 2002; Shiddamallayya et al., 2010). Furthermore, the antifungal effectiveness of *S. alata* has been established against *Epidermophyton floccosum* and *Trichophyton verrucosum.* Also, they possess anti-inflammatory potential (Saito et al., 2012; Lewis and Levy, 2011).

82.3.1 ANTIPYRETIC EFFECT

Timothy et al. (2012c) reported that pyrexia represents the most common symptoms of many deadly diseases. Many antipyretic agents are becoming less effective, costly, and toxic, thus the need to search for alternatives in plants containing natural bioactive molecules which are known to be cheap, easily accessible, and nontoxic. The authors reported that *Senna alata* contains many of these bioactive molecules like flavonoids, terpenoids, anthraquinones, and exhibited a strong antipyretic effect. These physiological effects produced by *S. alata* was suggested by the authors to be through suppression of temperature via vasodilation, decreased synthesis of prostaglandin. Meenupriya et al. (2014) reported that *S. alata* possess bioactive compounds like polyphenols and anthraquinones. Thus, the physiological activity of the plant is linked with the presence of biochemical constituents like phenols, saponins, tannins, alkaloids, flavonoids, steroids, and carbohydrates which are responsible for the antipyretic effects (Vedavathy and Rao, 1991).

Malaria is a parasitic infection caused by protozoan of the genus *Plasmodium* spp. and transmitted by Anopheles mosquito vectors. The antiplasmodial activity of *S. alata* inhibits *P. falciparum* growth due to the pharmacological action of many of the bioactive molecules present in it (Vieira and Skorupa, 1993). Kaempferol 3-O-sophoroside present in *S. alata* exhibited strong analgesic activity as reported by Meenupriya et al. (2014). Chemotherapy assessment of *S. alata* antimalarial activities could be associated with the presence of quinones, terpenes, and alkaloids in the extract. Quinones extracted from *S. alata* significantly displayed *in vitro* antiplasmodial activity against *Plasmodium falciparum*. Also, Terpenes extracted from *S. alata* leaves displayed massive *in vitro* antiplasmodial assays against *P. falciparum.*

82.3.2 CARDIOVASCULAR EFFECTS

Da et al. (2018) reported that *S. alata* leaves possess many natural phytochemicals such as flavonoids like quercetin, apigenin, myricetin, chrysin, alkaloid, saponin, tannin, phlobatannin, flavonoid, cardiac glycoside, emodin, phenolic acid, kaempferol, polyphenols like coumarins, tannins, xanthones, and many others terpenoid that perform inhibitory role on lipoxygenase (LOX) and cyclooxygenase (COX). The authors also pointed out that luteolin, 4,5,7-trihydroxy-2-methyl anthraquinone, oleic acid, palmitic acid, octadecanoic acid, and stearic acid are abundant in *S. alata*, and display a strong antioxidant role by inhibiting TNF-α, thus activation of the nuclear factor-kappa Beta through LPS and the stimulation of the activator protein-1. The genistein biomolecule inhibits the stimulation of NF-κB, STAT-1, iNOS expression and NO production. The gallic acid and flavonoids block the leukocyte migration by inhibiting the compliance to the vessel wall and inhibition of adhesion molecules such as ICAM-1, Eselectin, and VCAM-1 in the vascular endothelial. The tannins increase the capillary strength, reduces the capillary permeability, maintenance of collagen, inhibit phospholipase A2, leukotrienes, and prostaglandins.

Da et al. (2018) also reported that gallic acid and its derivatives from *S. alata* leaves have the capacity to inhibit stimulated p38 mitogen-activated protein kinases, NF-κB, histamine, IL6 and TNF-α. Abu et al. (2015) reported that *S. alata* aqueous leaves extract reduced oxidative stress in hyperglycemic condition by raising the antioxidants enzymes. Studies have shown that Diabetes mellitus (DM) is a metabolic disease described by

hyperglycemia because of deficiency in insulin secretion or insulin action. The authors showed that *S. alata* contains alkaloids, flavonoids, saponins, kaempferol that helps to prevent oxidative stress, cardiovascular diseases, and metabolic changes. Studies have also shown that Alkaloids have a microbiocidal role as antidiarrheal due to the effects on the small intestine, antihypertensive anti-inflammatory, antifungal, anti-fibrogenic effect.

Reezal et al. (2015) revealed that *S. alata* possesses bioactive ingredients that can be utilized for the treatment of hyperglycemia and other cardiovascular oxidative stress. Mohamed et al. (2015) revealed that *S. alata* extracts helps to fight against deadly cardiac Coxsackievirus B3 infections known to cause viral myocarditis. These physiological effects of *Cassia alata* extracts was possibly through reduction in morbidity, HW/BW, mortality, virus titers, mononuclear cell infiltration and necrosis. The authors suggested that the bioactive molecules present in the plant like achrosin, emodin, aloeemodin, anthraquinones, apigenin, anthrones, aurantiobtusin, cassiollin, campesterol, chryso-obtusin, chrysarobin, chrysophanic acid, chrysophanol, and chrysoeriol enables the cardioprotective and antiviral effects against CVB3 myocarditis.

82.3.3 NEUROLOGICAL EFFECTS

Da et al. (2018) reported that inflammation is the main cause of many local reactions in the body such as chronic auto-immune illness, cartilage erosion, edema, pain. The authors showed that *S. alata* possesses anti-inflammatory, analgesic, and antioxidant properties. Nkundineza et al. (2020) revealed that *S. alata* can be utilized as anticonvulsant and sedative effects. From their study, it was revealed that the central motor activity significantly reduced after *S. alata* administration. They noted that the plant contains alkaloids, saponosides, tannins, free anthraquinones and flavonoids. The authors pointed out that sedatives are generally utilized for anxiety and different nervous tension to relieve pain, insomnia, and relaxation. The authors found that *S. alata* leaves are utilized for fighting against anti-inflammation, fever convulsion, pain, cerebral malaria, epilepsy, anxiety, and dermatitis.

Villaseñor et al. (2002) revealed that *S. alata* leaves extract consist of bioactive molecules with capacity to decrease motor activity, hyperemia, enophthalmus, likewise causing paralysis, enophthalmus, screen grip loss, drooping with closure of the eyelids. Tologbonse et al. (2015) reported that *S. alata* root extract possesses pharmacological effects on the smooth muscle

activity. They suggested that this pharmacological activity is as a result of high level of bioactive ingredients in the plant such as anthraquinones, aloe-emodin, rhein, kaempferol, chrysophanol, physcion, flavonoid, and emodin.

Negedu et al. (2020) demonstrated the anti-nociceptic effects of *S. alata* in experimental rats through reducing the withdrawal latency thereby suppressing the peri-aqueductal gray matter to generate endogenous endo-peptides that flows to the spinal cord to inhibit the transmission of pain stimuli in the dorsal horn, thus blocking nociceptor stimulation.

82.3.4 ANTI-TUMOR EFFECT

The cytotoxic effect of ethanol extract of *S. alata* seeds and gallic acid using shrimp larvae have been reported (Awal et al., 2004). In another study, the cytotoxicity effects of *S. alata* extract was evident on Col 2, MCF-7 and T24 cancer cell lines (Olarte et al., 2013). F61, an isolate containing a blend of polyunsaturated fatty acid esters was found to possess anti-tumor property. This is via apoptosis (Olarte et al., 2013).

The anti-neoplastic effects of n-hexane *S. alata* leaves' extract on OV2008 cancer cells was attributed to kaempferol in another study (Levy and Shanna-kay, 2012). Hydromethanolic extract of *S. alata* leaves inhibited K562 leukemia cell (Adebesin et al., 2013). The anticancer effects of the seeds have been reported (Awal et al., 2004).

82.3.5 ANTI-INFLAMMATORY, ANTIULCER, AND WOUND HEALING EFFECT

Different leaf extracts of *S. alata* have been reported to exhibit varying degrees of anti-inflammatory effects. In a study in which butanol, ethyl acetate (EAE) and MEs of *S. alata* were tested on carrageenan-induced rat paw edema model, butanolic extract of *S. alata* leaf had the highest anti-inflammatory effects (Patrick-Iwuanyanwu et al., 2011).

In another study involving concanavalin A-induced histamine, 5-lipoxygenase inhibition and cycloxygenases, the heat-treated leaf extract showed a higher inhibitory effect at low concentration in comparison to sundried leaf extract (Moriyama et al., 2003). Furthermore, leaf extract of *S. alata* considerably reduced inflammation in CFA arthritic rats (Lewis and Levy, 2011).

Ethanol extract of *S. alata* leaves inhibited gastric lesions as indicated by reduced gastric volume, free acidity and ulcer index (Babu et al., 2012). *S. alata* enhanced healing of burns (Nasution et al., 2019).

82.3.6 ANTIOXIDANT EFFECT

Methanol and BHT extract of *S. alata* leaves showed antioxidant effect in a study (Panichayupakaranant and Kaewsuwan, 2004; Chatterjee et al., 2013). The antioxidant effect of the *S. alata* seed pod, flower, and root has also been reported (Fatmawati et al., 2020). In a study to compare the antioxidative potentials of methanol and n-hexane extracts of *S. alata* leaves, ME was found to be more effective than n-hexane extract. This could be attributed to the presence of kaempferol, butylated hydroxytoluene (BHT) and emodin. Furthermore, bioactive compounds including tocopherols, anthraquinones, carotene, ascorbic acid and flavonoids also enhanced the anti-oxidative ability of the extract (Oladeji et al., 2020). Aqueous extract of *S. alata* also minimized lipid peroxidation (LPO) and elevated the activity of catalase (CAT) (Oladeji et al., 2020). Reverse phase–solid phase extract of *S. alata* leaves showed a higher antioxidant capacity in comparison with ascorbic acid and trolox (Saito et al., 2012).

82.3.7 ANTIMICROBIAL ACTIVITIES

Several researchers have revealed that *S. alata* has effective antimicrobial metabolites which could be responsible for antifungal and antibacterial activity (Fuzellier et al., 1982; Khan et al., 2001; Timothy et al., 2012a, b). Timothy et al. (2012b) tested both aqueous and MEs of *S. alata* on the following fungal strains; *C. albicans*, *P. notatum*, *M. canis T. mentagrophtes*; there was maximum inhibition due to the increased concentration of the extracts (Khan et al., 2001; Makinde et al., 2007; Sule et al., 2011). They experienced a different antifungal activity with the leaves and Ketokonazole efficacy on *A. niger* and *P. notatum*. Makinde et al. (2007) reported that the varying antifungal effect could be due to the absence of polysaccharide in the plant extract. Timothy et al. (2012b) reported that there was greater inhibition with plant extract than conventional antibiotics on all tested organisms except for *A. niger*, but there was inhibited growth in *A. niger* upon application of aqueous extract.

Timothy et al. (2012a, b) revealed the possible cause for antimicrobial variation in the zones of inhibition width, which they said could be due to anthraquinone found in ethanol extract but was absence in aqueous extract. The result obtained during their work did not corroborate with the findings of Bharathidasan et al. (2011) who revealed that the ethanol extract of *S. alata* had antifungal activity at reduced concentration of the extracts on *C. albicans* when compared to *A. niger*. They concluded by reporting that *S alata* was found to show higher antifungal potency on several pathogenic fungal isolates that can cause human diseases.

Faruq et al. (2010) recorded increased inhibitory effect on tested organisms at increased concentration of the active components. They concluded that upon utilization of the bulk extract, the results were encouraging but after separation of the phyto-complexes, they found steroid to give wider zones of inhibition compared to when used in bulk and very effective on all tested organisms.

Makinde et al. (2007) recorded varying antimicrobial activity with the use of ME of *S. alata* during their work on both bacteria and fungi strains. The bark extracts of *S. alata* was effective on *C. albicans*. Abubacker et al. (2008) revealed that the water extract of *S. alata* had effect on the tested fungal stains. The plant extracts posed great activity on some pathogenic dermatophytes.

Alalor et al. (2012b) conducted a study on *S. alata* and tested the several extracts on various fungal strains and recorded that only *Penicillium* sp. was resistant to the plant extracts. Their findings were in conjunction to the study of Ibrahim and Osman (1995) and that of Adnan et al. (2011). The outcome of their study reveals that there was a wider zone of inhibition when greater concentration was applied compared to when a reduced concentration was being used. Their result was in corroboration with Reezel et al. (2002) who reported that aqueous and ME of *S. alata* demonstrated great antifungal activity so as to be used for antifungal agents.

Adnan et al. (2011) in their study, extracted oil from *S. alata* seed where the thrombolytic, cytotoxic along with antibacterial activity through *in vitro* systems. The chloroform extract (CE) of the seed oil was used to test for activity of antibacterial by means of disc diffusion technique where that extract revealed potent activity of antibacterial against both gram-negative and gram-positive bacteria. Extract of DMSO obtained from the seed oil was also tested for Brine shrimp dosage bioassay by means of Brine shrimp nauplii. The extract from the seed oil exhibited reasonable activity of thrombolytic against negative control (i.e., water). With respect to antimicrobial activities

of the plants, Studies by Sule et al. (2010) indicated that the ethanol extract of the plant exhibited the greatest inhibitory effect on *Epidermophyton floccosum* and *Trichophyton verrucosum*. Alalor et al. (2012a) investigated the antibacterial level of the aqueous and MEs obtained from sundried leaf part of *Senna alata* against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli,* and *Pseudomonas aeruginosa* revealed that the extracts were effective against microbial infections by *S. aureus* and *B. subtilis.* Other antimicrobial studies indicate that the plant inhibited *Klebsiella pneumoniae, Aspergillus niger Pseudomonas aeruginosa, Candida albicans, Escherichia coli*, and *Staphylococcus aureus* (Okwu and Nnamdi, 2011).

82.3.8 HYPOGLYCEMIC EFFECT

Senna alata, fondly known as candle bush flower, exhibit numerous health benefits. A study on the glucose lowering potency of the plant in diabetic rats showed that there was a decline in fasting blood glucose in experimental hyperglycemic rats, but no hypoglycemic effect was observed when the same was administered to healthy rats (Palanichamy et al., 1988). Varghese et al. (2013) in their investigation reported that the inhibitory effect of the crude extract on alpha-glucosidase activity was superior to acarbose. *In vitro* hypoglycemic study by Varghese et al. (2013) revealed that different fractions of the crude extract (water, n-butanol, chloroform, and petroleum ether) showed inhibitory effect against alpha-glucosidase in a threshold that was similar to acarbose. Decline in high fasting blood glucose occurred when aqueous leaf extract was given to streptozotocin (STZ)-induced diabetic rats (Reezal et al., 2015) through mitigation of LPO and enhanced antioxidant capacity.

Nanna et al. (2015) reported that fasting blood glucose and lipid profile normalized when aqueous extract of the plant was administered. The α-amylase and α-glucosidase inhibitory potentials of acetone, ethylacetate, and hexane extracts of *S. alata* were investigated Kazeem et al. (2015) investigated the alpha-amylase and alpha-glucosidase inhibitory prowess of orally administered acetone, ethylacetate, and n-hexane extracts of the plant in sucrose-induced hyperglycemia. They discovered that while acetone exhibited the greatest inhibitory effect against alpha-amylase, hexane extract showed the peak inhibition to alpha-glucosidase noting that within two hours, hexane extract elicited a fall in glucose level after meal. There is the claim by traditional herbal medicine practice that *S. alata* flower is efficient

in the management of diabetes. Uwazie and colleagues recently confirmed the anti-diabetic potential of *S. alata* in alloxan-induced diabetic rats. The study revealed that *S. alata* ameliorated diabetes induced glucose dysregulation and dyslipidemia. The anti-diabetic effect of *S. alata* is associated with repletion of liver glycogen content as well as increased glucose-6-phosphate dehydrogenase and hexokinase (HK) activities (Uwazie et al., 2020).

Interestingly, Uwazie et al. (2020) also reported that *S. alata* have beneficial effect on the cardiac tissue through the suppression of diabetes induced increased computed cardiac index, coronary index and atherogenic index. This suggests that along with its anti-diabetic potential *S. alata* can prevent the cardiovascular complications of diabetes that may be very debilitating, deadly, and financially draining (Uwazie et al., 2020). The finding of Uwazie and coworkers is in line with the previous report of Yakubu et al. (2016) which demonstrated that aqueous extract of *S. alata* flower possess anti-diabetic properties through its ability to lower elevated fasting blood glucose levels together with elevated HK activity.

82.3.9 HYPOLIPIDEMIC

Works on the hypolipidemic effect of water extract of *Senna alata* in experimental exogenous lipid-induced obesity in rats at 250 mg/kg and 500 mg/kg/day showed suppression of hepatic phosphoenolpyruvate carboxykinase proteins and glucose-6-phosphatase (G6Pase) as well as upregulation of muscular glucose transporter 4 (GLUT4) and hepatic and muscular adenosine monophosphate-activated protein kinase phosphorylation (pAMPK) (Naowaboot et al., 2017). Ethanol extract of the plant at doses of 500 mg/kg–2,500 mg/kg was reported by Onyegeme-Okerenta (2017) to depress an elevation in fasting blood glucose, total cholesterol (TC), triglyceride, and low-density lipoprotein in diabetic rats.

82.3.10 ANTI-OBESITY AND GLUCOREGULATORY EFFECT

The improved glucometabolic and insulin sensitivity regulation of *S. alata* was demonstrated in high-fat-fed mice. The *S. alata* extract at 250 and 500 mg/kg exhibited hypoleptinemia, hypoglycemia, and decreased circulating insulin level in high-fat-fed mice (Naowaboot and Piyabhan, 2016). Impaired glucoregulation induced in obese mice fed with a high-fat diet (HFD) was reversed by *S. alata* treatment (Naowaboot and Piyabhan, 2016). The *S. alata*

extract demonstrated an anti-obesity effect in high fat-fed mice by decreasing adipocyte size, epididymal fat weight, TNF-α and monocyte chemoattractant protein-1. In addition, *S. alata* extract led to increased circulating adiponectin, reduced phosphoenolpyruvate carboxykinase, and G6Pase proteins in the high fat-fed obese mice while the *S. alata* extract caused elevated muscle GLUT4 and increased adenosine monophosphate-activated protein kinase phosphorylation in the muscle and liver tissues of the obese mice suggesting that the improved glucometabolic regulatory function of the *S. alata* extract is through suppressed liver gluconeogenesis and enhanced glucose utilization through up-regulation of the adenosine monophosphate-activated protein kinase (Naowaboot and Piyabhan, 2016).

KEYWORDS

- **antiplasmodial activity**
- **antipyretic effect**
- ***Cassia alata***
- **monophosphate-activated protein kinase**
- **pharmacology**
- ***Senna alata***

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CHAPTER 83

Pharmacology, Photochemical, and Healing Effectiveness of *Chromolaena odorata* (L.) R.M. King & H. Robinson

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83.1 INTRODUCTION

Chromolaena odorata (L.) R.M. King & H. Robinson, of the family of Asteraceae, is a perennial shrub that is found in the subtropical and tropical regions where it grows rapidly. It is commonly known as Siam weed. It is one of the American native plants that have invasively spread to sub-Saharan

Africa, Asia, and Oceania. Synonyms of the plant include *Eupatorium odoratum* L., *Eupatorium conyzoides* Mill, *Eupatorium divergens* Less., *Euptorium floribundum* Kunth. Despite the incursive nature of *Chromolaena odorata*, it has a wide variety of ethnomedicinal and pharmacological applications. Numerous phytochemicals have been isolated from its leaves, soft stems and woody base which are used extensively by traditional healthcare practitioners to manage, prevent, and treat various infections and diseases (Omokhua-Uyi et al., 2020; Oladipupo et al., 2015; Kouamé et al., 2013; Putri and Fatmawati, 2019).

83.2 BIOACTIVE COMPONENTS

Oladipupo et al. (2015) reported the strong insecticidal, larvicide, and ovicide activities of *Chromolaena odorata*. The presence of essential oils (EOs) like β-caryophyllene, bicyclogermacrene, germacrene-D, geijerene, α-pinene, (Z)-β-farnesene, pregeijerene, limonene, camphor, chalcolnes, and flavonones, kaurane-type diterpenoids, alkaloids were fingered to account for the observed activities. Furthermore, volatile insecticidal constituents in *Chromolaena odorata* were characterized as δ-cadinol, γ-eudesmol, ledol, dodecyl acetate, widdrol, carotol, caryophyllene oxide, viridiflorol, palustrol, spathulenol, α-elemol, γ-cadinene, δ-cadinene, trans-γ-bisabolene, 2,5-bis-(1,1-dimethyl) phenol, α-muurolene, viridiflorene, α-bulnesene, germacrene D, α-amorphene, α-humulene, γ-muurolene, thujopsene, γ-elemene, trans-α-bergamotene, vanillin, β-caryophyllene, α-copaene, β-elemene, citronellyl acetate, eugenol, α-cubebene, undecanal, carvone, piperitone, β-citronellol, myrtenol, isopulegol, α-terpineol, cis-verbenol, trans-pinocarveol, m-cresol, cis-linalool oxide (furanoid), 1, 8-cineole, δ-3-carene, β-pinene, and limonene.

Kouamé et al. (2013) isolated three compounds from the fraction of *Chromolaena odorata* leaves using hexane which corroborated two previously isolated compounds; 5-hydroxy-4,7′-dimethoxyflavanone from leaf extracts (Iwu and Chiori, 1984; Wollenweber et al., 1995; Pisutthanan et al., 2006), and 2′-hydroxy-4,4′,5′,6′-tetramethoxychalcone from the leaves in n-hexane (Bose et al., 1973; Suksamrarn et al., 2004; Wafo et al., 2005). The third isolated compound was identified spectroscopically as 1, 6-dimethyl-4-(1-methylethyl) naphthalene (cadalene) which is a pale-yellow oil.

Recently, Putri and Fatmawati (2019) identified a new flavanone compound 6′-dimethoxyflavanone (odoratenin), and 5,3′-dihydroxy-7 with two compounds that are already known: isosakuranetin and subscandenin obtained from the leaves of *Chromolaena odorata* in East Indonesia region. Omokhua-Uyi et al. (2020) recently revealed that the South African siam weed has some flavonoids that include pectolinaringenin, (±)-4′,5,7-trimethoxy-flavanone, 4′-methoxykaempferol (3,4,7-trihydroxy-4′-methoxyflavone), and tri-O-methylkaempferol. More phytoconstituents from the weed are chromomoric acid, quercetin, eupatilin, acacetin, luteolin, and chalcone.

Emani et al. (2015) in their work, reported *C. odorata* to have secondary metabolites of about 21 types like 3,2′-dihydroxy-4,4′,5′,6′-tetramethoxychalcone, chalcone, three novels of flavanone. Most of these isolated compounds showed effective anti-adipogenesis and antioxidant activities.

Meutia (2019) noted that different portions of the plant are usually utilized for the treatment of burns, wounds, cancer, skin infections, hepatotoxicity, diabetes, microbial infections, and have antioxidant as well as anti-inflammatory properties. Most of the therapeutic potentials of *C. odorata* depend on their bioactive constituents. The dried plant was studied and observed to consist of flavonoid aglycones (flavones, flavonols, flavanones) such as chalcones, acacetin, luteolin, eupatilin, kaempferol, naringenin, quercetagetin, quercetin, along with terpenes, terpenoids as well as sinensetin, phenolic compounds and other EOs, which is responsible for physiological action in our body.

83.3 PHARMACOLOGY

Elion Itou et al. (2017) reported that *Chromolaena odorata* possess analgesic, antipyretic, and anti-inflammatory properties. They attributed the physiological properties to the presence of saponins, cardiotonic-heterosids, alkaloids, terpenoids, tannins, and steroids.

83.3.1 ANTIPYRETIC EFFECT

Vanita and Sana (2018) reported the potent antipyretic effects the plant which is caused by the abundant phytochemical presence. Some of the active biomolecules are EOs, terpenes, and terpenoids, saponins, tannins, flavonoid aglycones (flavonols, flavanones, flavones) naringenin, quercetin,

kaempferol, acacetin, eupatilin, chalcones, luteolin, sinensetin, and quercetagetin. Oludare et al. (2000) also lend credence to the use of the fractions of flavonoid in *C. odorata* as analgesic, antipyretic, and anti-inflammatory acknowledging its ethnobotanical values which are impelled by flavonoids, isosakuranetin, sakuranetin, and quercetin molecules.

83.3.2 CARDIOVASCULAR EFFECTS

Osa et al. (2015) assessed the physiological role of *Chromolaena odorata* on liver enzymes and serum metabolites. From their finding, they discovered that consumption of *C. odorata* is very safe and nontoxic with tremendous cardiometabolic health benefits like hypocholesterolemia and reduced coronary heart diseases. *C. odorata* was analyzed and showed the presence of bioactive metabolites such as saponins, alkaloids, cyanogenic glycosides, tannins, and electrolytes. Studies have shown that flavonoids can inhibit the 5-lipo-oxygenase and cyclo-oxygenase implicated in many cardiovascular diseases. Thus, the findings of Asomugha et al. (2013) that *C. odorata* could be beneficial in protecting coronary heart disease. More so, the administration of *C. odorata* was noted to significantly decline bleeding diathesis with hemostatic properties (Henshaw et al., 2016). Hence, *C. odorata* significantly decline the clotting period and stimulate platelet quality, a property linked with the presence of tannins, saponnins with precipitating, coagulative, and hemostatic effects.

Thaddée et al. (2015) linked the immunomodulatory and antioxidant properties of *C. odorata* to the polysaccharides presence in the extract. Their studies revealed that polysaccharides such as lentinan, krestin, and schizophyllan also have biological activity potentially valuable in the treatment of disease conditions like malaria, inflammation, atherosclerosis, hypertension, pain, cellular degeneration and wounds. High level of sterols, polyphenols, polyterpenes, tannins, alkaloids, saponins, and polysaccharides like phenolic, sugar, hemicellulosic, protein, arabinogalactans proteins, and pectic are also found in *C. odorata*. Natural antioxidants of plants are usually considered as prospective therapeutic agents in the management of many diseases caused by oxidative stress like cardiovascular and metabolic diseases. Umukoro et al. (2006) observed that *C. odorata* extract displays significant membrane stabilizing property against hemolysis and PAF receptor-binding blocking ability exerting effective cardiovascular function.

A significant and potential reducing effect of *C. odorata* on the cardiovascular risk factors was reported by Ogbonnia et al. (2010). They however observed that chronic exposure to the extract at high dose may have deleterious outcome on the blood vessels and the heart. Jude and Catherine (2011) associated *C. odorata* aqueous extract with anti-cholesterolemic activity and potential for the reduction of cardiovascular risk. It has been observed that dyslipidemia may accompany hypertension, obesity, and DM due to increase in the level of plasma LDL-C, triglycerides, and total-VLDL-C and reduced HDL cholesterol. These cholesterol lowering effects have been linked to high amounts of saponins. Similarly, aqueous leaf extract of *C. odorata* reduced salt-loading induced dyslipidemia and cardiomegaly. Further studies revealed that hypercholesterolemia contributes to the progression of hypertension via reduced NO production, increased renin-angiotensin-aldosterone system activity, increased vasoconstriction molecules, increased endothelin, increased cholesterol, reduced membrane fluidity and ion channel activity. Thus, *Chromolaena odorata*'s bioactive molecules have been shown to promote cardioprotective properties, reduce the plasma triglyceride levels and cardiovascular complications.

Cardiac hypertrophy and hyperlipidemia are risk factors for cardiovascular diseases that usually develop due to hypertension. Ikewuchi et al. (2014) demonstrated that *C. odorata* extract ameliorated the cardiovascular impairment induced by salt loading in rats. The protective effect of *C. odorata* extract in the heart is seen in its ability to reduce cardiac hypertrophy induced by salt loading hypertension indicating an interesting evidence of anti-hypertensive potential of *C. odorata* extract (Ikewuchi et al., 2014). Also, the salt loading model is associated with dyslipidemia which was attenuated by *C. odorata* extract suggesting that *C. odorata* may have endothelial and vascular protective effects because excess lipid accumulation has been reported to be associated with impaired endothelial function, low NO bioavailability and arterial stiffness (Ferrier et al., 2002; Sposito, 2004).

83.3.3 NERVOUS SYSTEM EFFECTS

Dougnon and Ito (2021) reported that terpenes and sesquiterpenes present in *C. odorata* essential oil is important for several physiological activities particularly sedative activity in the central nervous system (CNS) through association with cholinesterase inhibitor, noradrenergic system and several folds of direct association with the GABA system, GABA-gated chloride

channels blockade, antagonistic, and agonistic, allosteric, and straight binding to $GABA_A$ receptors. This suggests that the plant possesses several metabolites affect the peripheral and CNS. These bioactive metabolites can be further sub-grouped into diverse distinct groups based on synthetic pathways or chemical structure. The most prevalent biomolecules are the alkaloids, phenolic compounds and terpenes. Inflammation is known to up-regulate several pro-inflammatory cytokines and enzymes like COX-2 and inducible nitric oxide synthase (iNOS) producing pro-inflammatory intermediaries like NO, interleukin-1β (IL-1β), tumor necrosis factor (TNF)-α, and prostaglandin E2 (PGE2) shown to be capable of inhibiting inflammation *in vivo* and *in vitro* due to the availability of triterpenes, flavonoids, biomolecules, alkaloids.

83.3.4 ANTIOXIDANT ACTIVITY

In 2016, Samuel et al. affirmed that the hydromethanol extract of *C. odorata* leaf showed significant antioxidant and analgesic activities in rodents because of its phytochemical compounds like alkaloids, terpenes, saponins, steroids, flavonoids, glycosides as well as tannins. Thus, ameliorating the pain sensation that was experimentally induced using acetic acid writhing through inflammatory response that caused the production of arachidonic acid from phospholipid and production of prostaglandins from cyclooxygenase (COX).

The biological properties such as anti-oxidative, cytotoxic effects, and anti-inflammatory activity of *C. odorata* are linked to bioactive constituents like polyphenols, alkaloids, tannins, soluble polysaccharides, sterols, and saponins (Boudjeko et al., 2015). Bioactive compounds including dauca-5, 8-diene, pregeijerene, β-pinene, caryophyllene, and α-pinene were detected as principal components of essential oil from *C. odorata* leaves (Pitakpawasutthi et al., 2016). A new flavanone, odoratenin as well as isosakuranetin and subscandenin were equally biofunctional compounds isolated from *C. odorata* (Putri and Fatmawati, 2019). Furthermore, immunomodulatory activity and free radical mopping properties of this plant were consequent upon the activation of PBMC (peripheral blood mononuclear cells) as well as IFN-γ (interferon-gamma) synthesis (Boudjeko et al., 2015).

Chromolaena odorata possess several antioxidant activities which have made it more versatile worldwide. Phan et al. (2001a) identified the antioxidant effect of *C. odorata* using fractions that were purified on cultured

fibroblast and keratinocytes. This resulted in identification of phenolic acid such a ρ-coumarine, vanillic acid, ferulicprotoatechuic, and ρ-hydroxybenzoic together with the complex mixtures of flavonoids which are hydrophobic in nature such as flavones, flavanononones, chalcones, and flavonols from the plant. Also, a comparative *in vitro* investigation between the polyphenolic and ethanol extracts from the plant leaves of *C. odorata* was reported to produce higher regeneration of fibroblast endothelia cells together with keratinocytes which confirms the antioxidant effect of polyphenolic and ethanol extracts on hypoxanthine and hydrogen peroxide induced damage to human keratinocytes as well as fibroblast (Phan et al., 2001c). Furthermore, the extract has NO scavenging activity which was quantitatively determined by the total phenolic content (Alisi et al., 2008). Powerful antioxidant activity was established in a comparative study between the methanol leaf extracts of *Ficus religiosa* L., *Cynodon dactylon* (L.) Persoon and *Chromolaena odorata* (Melinda et al., 2010). The extracts of methanol and ethanol of *C. odorata* showed free radical scavenging activity and therefore exhibited strong antioxidant properties (Bhargava et al., 2013). While relatively low values of antioxidant indices were observed for *C. odorata*, it is still greatly used in folklore medicine with documented successes (Akinmoladun et al., 2007). The *in vitro* CE activity of the plant clearly indicates a significant antioxidant activity and support its potential application as an antioxidant agent (Rao et al., 2010). Also, studies have shown higher level of antioxidant activity in the ethanol extract of *C. odorata* leaf and *Annona squamosa* seed (Vijayaraghavan et al., 2013). In a recent investigation, the assessment of the polysaccharide fraction of the leaves and the hemicellulose fraction of *C. odorata* and *Allanblankia fluoribunda* stem bark showed remarkable scavenging of free radicals using DPPH and ABTS in a manner that was dose dependent (Boudjeko et al., 2015).

Uhegbue et al. (2016) assessed the antioxidant and lipid lowering potential of combination of *Ageratum conyzoides* and *C. odorata*. They reported a synergy in the reduction in hypoglycemic and lipid lowering markers including peroxidation of lipid, cholesterol, and triacylglycerol.

83.3.5 ANTI-INFLAMMATORY ACTIVITY

Chromolaena odorata is composed of chromomoric acid (C-I) and phytoprostane 1 which stimulated nuclear factor-erythroid 2-related factor 2 (Nrf2) which inhibits inflammation (Heiss et al., 2014). There are indications that

*C. odorata*s use in the treatment of inflammatory conditions including pile, sore throat and burns (Kigigha and Zige, 2013). Gout is an inflammatory metabolic disease with a high global prevalence rate. Allupurinol, a xanthine oxidase inhibitor is common therapy with considerable side effects (Kikiowo et al., 2020). There is evidence that *C. odorata* flavones scaffold possesses better inhibitory potentials as well as minimal side effects in comparison with allupurinol in the management of gout (Kikiowo et al., 2020).

Studies have affirmed the presence of various analgesic, anti-inflammatory, and antipyretic agents in *Chromolaena odorata*. Using various animal models for tests, such as Brewer's test for the antipyretic potential, and formalin paw as well as hot plate for the determination of analgelsic potential (Umukoro et al., 2006). In another experiment, the anti-inflammatory potential of *C. odorata* was linked to flavonoids in the organic extract (Pisutthanan et al., 2005). Furthermore, Owoyele et al. (2005) studied the aqueous extract of the plant and observed that it was capable of reducing the inflammatory activity due to edema induced by formalin in rats. It has been documented in a related study that the six fatty acids which include (S)-coriolic acid, (S)-15, 16-didehydrocoriolic acid, (S)-coriolic acid methyl ester, and linolenamide, (S)-, linoleamide, and 15, 16-didehydrocoriolic acid methyl ester were isolated from *C. odorata*. These were able to bring about the inhibition of production of NO in desired concentration (Hanh et al., 2011). In another study, the mechanism of anti-inflammation of the extract of *C. odorata* extract as well as its bioactive agents scutellarein tetramethyl ether showed an alteration of NF-kB route hence showing their applications in anti-inflammatory connected ailments (Pandith et al., 2013a).

83.3.6 WOUND HEALING AND HEMOSTATIC EFFECTS

Ayyanar and Ignacimuthu (2009) in their work reported the use of paste prepared from grounded *Chromolaena odorata* leaves in the treatment of wounds so as to hasten the healing. Similarly, Raina et al. (2008) reported the use of ointment prepared from the leaf extract of the same plant in the enhancement of the regeneration of endothelial and fibroblast cells in injuries. This supported the wide use of the plant in hastening the healing process of burns and wounds. Phan et al. (2001b) investigated the *in vitro* potentials of some phenol components like vanillic acids, protocatechuic, p-hydroxybenzoic, and p-coumaric obtained from *C. odorata* which protected cultured skin against oxidative stress.

Akah (1990) reported that the plant's hemostatic action could be attributed partly to the *C. odorata* vasoconstriction effect on the receptor. The wound healing ability of *C. odorata* extract has been reported. Sirinthipaporn and Jiraungkoorskulin (2017) observed that the plant is rich in antioxidant content, cause inhibition of pro-inflammatory factors as well as antibacterial effect, which inhibits infections. Other wound healing mechanisms of *C. odorata* include the induction of haeme oxygenase-1 in the fibroblasts, the induction of thromboxane synthase as well as suppression of matrix metalloproteinase-9 (MMP-9) (Pandith et al., 2013b).

C. odorata also enhanced keratinocyte migration, stimulation of extracellular matrix proteins as well as basement membrane constituents (Sirinthipaporn and Jiraungkoorskul, 2017). The expression of laminin-5, collagen IV, fibronectin, and laminin-1 were also upregulated by this plant extracts (Phan et al., 1998). In a study designed to examine the wound healing potentials of *C. odorata* extract at 2.5, 7.5, and 10% w/w of the extract ointment was administered on wounded rats for two weeks. The outcome was a varying degree of healing based on the induction of wound contraction and closure time (Pandurangan et al., 2015).

C. odorata aqueous extract expresses higher hemostatic activity than the ethanol extract (Anyasor et al., 2011). Significant decline in the bleeding and clotting times was observed in rats orally administered with *C. odorata* extract for two weeks. This was due to its platelet's formation and activation potentials (Akomas and Ijioma, 2014).

83.3.7 ANTI-ULCEROGENIC EFFECT

The anti-ulcer effect of *C. odorata* has been reported. In a study, significant improvement was observed in rat induced with gastric ulcer and administered with *C. odorata* aqueous extract converted to spray dried powder. This was indicated by an increase in platelet count, inhibition of gastric bleeding as well as protection of thromobytes (Paul et al., 2018). The antiulcerogenic effect of *C. odorata* was associated with its rich content of phytochemicals including polyphenols and flavonoids.

83.3.8 ANTICANCER ACTIVITY

Some phytochemicals such as dimethoxyflavanone, cadalene, and tetramethoxylchalcone were isolated and characterized from *C. odorata* were

shown to have anticancer potency and higher efficacy on the clonogenecity of the cancerous cells line (Kouame et al., 2013). The findings from the study showed that the various compounds that were isolated had remarkable anticlonogenic and cytotoxic potency at 20 um in cell line and this was also observed to act alongside the barium chloride inhibitor in enhancing apoptosis in the breast cancer cells. A related study revealed that ME from the leaf had high activity against lung cancer cells (Adedapo et al., 2016). ME of *C. odorata* inhibited HT29 cancer cells after 72 hours of administration. Furthermore, there was an interference of the extract with VEGF (vascular endothelia growth factor) and endothelin-1 (E-1) (Adedapo et al., 2016).

83.3.9 HEPATOPROTECTIVE ACTIVITY

It has been reported that extracts obtained from *Chromolaena odorata* has unique potencies against ulcer when used orally together with honey (Nur Janah et al., 2006). In another study, ethanol extract from the leaf was used for *in vitro* investigation in assessing its potential protective effect against liver damage resulting from oxidative stress induced by carbon tetrachloride. When this plant was employed for pretreatment, the results showed a remarkable protection of the liver against damage (Alisi et al., 2011). Asomugha et al. (2014) also established that the plant aqueous extracts was also capable of protecting the liver.

Atindehou et al. (2013) isolated and identify two bioactive components from the extracts of *Chromolaena odorata* which also showed higher activity against bacteria. These bioactive agents include sinensetin and scutellarintetramethyl ether. The solvents used for these extractions include butanol, cyclohexane, ethylacetate, and dichloromethane (DCM). Suksamrarn et al. (2004) reported some bioactive components from the extract of flower of *C. odorata* that include chalcones, tetramethoxyflavanone, acacetin, luteolin, persicogenin, and isosakuranetin.

When the isolated compounds were investigated further, it was observed that they exert moderate to weak inhibition against *M. tuberculosis* with MIC (minimum inhibitory concentration) values that vary. A similar study carried out on the extract of the leaves using ethanol as solvent, revealed a remarkable inhibition against *P. aeruginosa* and high antibacterial activity at 8.0 mg/ml for *P. aeruginosa* which is gram-negative bacteria, and *Streptococcus faecalis* which is gram-positive (Irobi, 1997).

The shrub therefore has antimicrobial potential which played a key role in its wound healing process. In an experiment that was conducted using DCM as extractant, a higher antimicrobial potential was noted against *Staphylococcus* spp. (Ling et al., 2007). In a similar work, it was documented that a total of 10 flavonoids that were derived from *C. odorata* ME strong potency to three multi resistant strains of *Staphylococcus aureus* (Johari et al., 2012). This therefore suggests the plant's possibility to be used in enhancing efflux inhibitors. Kigigha and Zige in 2013, found that ethanol extract of *C. odorata* has antibacterial properties against *E. coli* and *S. aureus*.

Stanley et al. (2014), corroborated the anti-microbial potential of ethanol leaf extract of the plant against *S. aureus, Candida albicans*, and *Escherichia coli* which are clinical pathogens. It was further observed that the methanol leaf extract was more effective on gram-positive bacteria than the methanol stem extract. Also, the ethyl acetate (EAE) and MEs showed remarkable antimicrobial activity against the various gram-positive bacteria (Naidoo et al., 2011).

Omokhua-Uyi et al. (2020) established the anti-adhesion, anti-biofilm, and metabolic activities of *C. odorata* shrub against various diseases causing microorganisms such S*taphylococcus aureus*, *Cryptococcus neoformans*, and *Klebsiella pneumoniae*.

83.3.10 ANTIPARASITIC ACTIVITY

In vitro and *in vivo* studies of *C. odorata* confirmed the presence of quercetin-4-methyl ether in the leaf extract which showed remarkable activity against *Plasmodium falciparum* that are resistant to chloroquine. The study showed that gradient fraction of DCM was effective in the suppression of *P. falciparum* infection by 99.46 to 100 $mgkg^{-1}$ body weight (Ezenyi et al., 2014). The nematocidal potential of the leaf was established in an *in vivo* study, showing an alkaloid (dehydropyrrolizidine) from the root extract to be responsible for the nematocidal effect observed (Thoden et al., 2007).

83.3.11 ANTIMICROBIAL ACTIVITY

Tiwari et al. (2011) documented that *C. odorata* extract has antibacterial potentials due to increased complexes of flavonoid and phenol. They also reported that the polarity of the solvents used may be a contributing factor to the effectiveness of the plant extract. The nature of the secondary metabolites,

e.g., rutin, chrysin, and catechols, in the extracts may be equally responsible for its antimicrobial potency (Tiwari et al., 2011). Furthermore, insight into the activity of the antimicrobial complexes inhibition of pathogenic microorganisms was attributed to their capacity to bind to the cell membrane of the bacteria resulting in the disruption of synthesis of cell membrane (Lavanya and Brahmaprakash, 2011).

Stanley et al. (2014) examined *C. odorata* extracts on several gram-negative and positive bacteria and discovered the same result for all the four (4) extracts used. This confirmed the observation from Naidoo et al. (2011) report. Differences in antimicrobial actions of this plant extracts were related to the reduction in the quality of *C. odorata* upon extraction which may be linked to biotic and abiotic factors, the location of the plant, and the nature of the solvent used (Tiwari et al., 2011). Ethanol and MEs yielded great zones of inhibitions on typed strain *S. aureus. C. odorata* extract was found to be effective against gram-positive bacterial strains in comparison with gram-negative bacterial strains.

Hridhya and Kulandhaivel (2017) assayed the antimicrobial potency of *C. odorata* on some pyogenic microorganisms and discovered that only the ethanol extract showed wider inhibition zones in the test organisms. When the inhibition zone of *C. odorata* extracts were compared with conventional antibiotics, the results showed that *C. odorata* constituents were more effective than the conventional antibiotics. The presence of some phytocomponents were responsible for the antimicrobial effect of the plant extracts, this could be due to the insertion of the phytocompounds between the planar basses of the DNA thereby meddling with the division of cells (Tsuchiya et al., 1996; Doss et al., 2011). The presence of tannins in *C. odorata* extracts was found to precipitate the protein in the microbial cells and inactivate microbial attachment. Thus, the presence of bioactive complexes in the extracts of *C. odorata* makes it very proficient and effective against pyogenic bacteria. Also, the reduced pH level of the plant extract reduced the microbial population to the barest minimum since acidic pH environment has hypothetically lethal effect on the microbial population. A synergistic test of the extract showed an antifungal activity on the tested fungal strains (Umeze and Abarikwu, 1986). During the research work of Nurul-Huda (2004), *C. odorata* acted as a prospective antimicrobial agent against gram-positive strains with times of exposure using its polyphenolics extract *S. epidermidis*, and *S. aureus.*

Ngono et al. (2006) also carried out the antimicrobial effectiveness of hydroethanol extract of *C. odorata* showed its ability to obstruct the

growth of microbes such as *Trichophyton mentagrophytes, Crypococcus neoformans* and *Trichophyton rubrum* with a low MIC within range of 62.5–500 $mgml^{-1}$ extract and within 25–100 $mgml^{-1}$ fraction (Ngono et al., 2006).

The ethanol extract of the plant was shown to exert a strong inhibition against standard strains of microorganism (Irobi, 1997). Omokhua et al. (2017) evaluated the leaf extract antimicrobial activities of the two plant types against different strains of microorganisms, they discovered that Asian/African biotype possessed the highest antibacterial effect while South Africa biotype has the greatest antifungal effect. Omeke et al. (2019) indicated that ME of the plant at high concentrations was strongly inhibited *P. aeruginosa* isolates. Yaouba et al. (2017) assessed the relative effectiveness of ethanol extract of the plant over the aqueous extract as far as inhibition of EJD16 isolate growth on tomato fruits was concerned. Srisuda et al. (2016) reported the effectiveness of *C. odorata* extract on human skin infection due to bacteria. In their study, it was discovered that the high level of bioactive compounds such as phenolic and bioflavonoids present in the extract could be attributed to the physiological activities against the bacteria associated skin infection.

83.3.12 ANTICONVULSANT ACTIVITY

The anticonvulsant properties of *C. odorata* leaf extract has also been shown to be effective when tested in animal models (Amazu et al., 2013) even though literature and studies seem apparently scarce.

83.3.13 ANTIDIABETIC ACTIVITY

Investigations on anti-cataract and anti-diabetic impacts of ethanol extract of *C. odorata* leaf in diabetic rats revealed that the introduction of the plant orally brought about a remarkable decline in the uptake of glucose by the muscles of the skeletal region, enhanced tolerance of insulin and glucose, and also led to higher uptake of glucose by serum insulin (Onkaramurthy et al., 2013).

Related studies further carried out showed a decline in the formation and extent of the cataract. The findings revealed a reversal of the diabetic condition and cataract in the rats that were induced by streptozotocin (STZ). It

was also reported by Ijeoma et al. (2014) that ethanol extract obtained from the leaves of the plant showed hematologic, hypoglycemic, and lipid profile impact in diabetic rats of alloxan induction.

Omonije et al. (2019) documented a progressive decline in high fasting blood glucose associated with experimental diabetic rats with the greatest effect observed in 600 mg/kg body weight dose. They also noticed that at doses of 300 mg/kg and 600 $mgkg^{-1}$ body weight, elevated levels of total the biochemical markers (bilirubin, alkaline phosphatase (ALP), total protein (TP), aspartate transaminase, alanine transaminase, albumin) were normalized in experimental diabetic rats. In diabetic rats, administrations of 200 mg/kg and 400 $mgkg^{-1}$ body weight doses of ethanol extract of *C. odorata* leaf over a period of eight weeks elicited a decline in high fasting blood glucose, and lipid profile through enhanced muscular glucose uptake, improved circulating insulin, enhanced insulin and glucose tolerance, improved antioxidant strength and blunted oxidative stress markers (Mohammed et al., 2018). After 21 days of treatment with ethanol leaf of *C. odorata* at a dose of 300 mg/kg body weight, a glucose reducing effect in comparison with the standard drug was observed (Ijioma et al., 2014). In addition, there was a decline in the serum levels of very low-density lipoprotein, total cholesterol (TC), low density lipoprotein and triglyceride but there was an elevation in high density lipoprotein (HDL) level. Ethanol leaf extract of the plant at doses of 5 mg/kg–250 mg/kg body weight led to a glucose lowering effect with between 7^{th} day and 28^{th} day of administrations (Marianne et al., 2014). Exposure to 400 mg/kg dose of plant extract prior to carbon tetrachloride induced liver damage led to reversion of high serum levels of aspartate transaminase, lactate dehydrogenase, total bilirubin and alanine transaminase (Alisi et al., 2011). *Chromolaena odorata* leaf meal extract at increasing dose depressed and low-density lipoprotein, triglyceride, and TC but elevated serum urea level in rabbits (Osa et al., 2015). Conversely, treatment with aqueous leaves extract repeatedly at a dose 20 $mgkg^{-1}$ body weight four times per day caused a decline in TP as days advanced but albumin and bilirubin increased (Nwachukwu et al., 2015). This result warns against abuse and overdose of the extract. In addition, Asomugha et al. (2014) reported that administration of high dose might have negative health effects. In petrol intoxicated rats, a combination of aqueous and ethanol extracts suppressed serum concentrations of alanine transaminase, ALP, and aspartate transaminase (Achuba and Offor, 2020).

83.3.14 ANTIDIARRHEAL ACTIVITY

Apart from the fact that *Chromolaena odorata* has invasive properties, it has also been documented to have remarkable antidiarrheal qualities. Extracts of the leaves were prepared in a study using various solvents and tested against four different strains of critical diarrheal, i.e., *Vibrio, Klebsiella oxytoca, Shigella sonnei,* and *Salmonella enterica.* This showed that the antibacterial potencies were from 0.156–1.25 mgml^{-1} (Atindehou et al., 2013).

Two antibacterial groups were obtained from the isolation process, and characterization of the extracts obtained from *Chromolaena odorata* leaf, which include scutellarein tetramethyl ether and sinensetin and these, were found to show potency against the diarrheal strains. Aba et al. (2015) documented that *C. odorata* ethanol extract showed a high protection against diarrhea induced by castor oil and this was found to be dependent on dose.

KEYWORDS

- **antibacterial groups**
- **cardiovascular effects**
- **central nervous system**
- ***Chromolaena odorata***
- **hemostatic effects**
- **matrix metalloproteinase-9**

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CHAPTER 84

Phytochemical Constituents and Medicinal Effectiveness of *Buchholzia coriacea* Engl.

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84.1 INTRODUCTION

Mbata et al. (2009) demonstrated that across the globe, traditional medicine is gaining more relevance due to their accessibility, and effectiveness in prevention, diagnosis, and treatment of many diseases. Medicinal plants are plants with bioactive molecules capable of therapeutic benefits and also serve as food for mankind or as precursor to drug formulation. Many communities over the years have solely depended on traditional medicine as their major source of food and medicine. One of the notable plants utilized for the management of several diseases is *Buchholzia coriacea* Engl. recognized for its effectiveness due to the presence of several phyto-active ingredients. This plant is widely distributed across Africa, and currently utilized as antioxidant, anti-inflammatory, antimicrobial, antihelmintic, antihypertensive, antimalarial, anticancer, abortifacient, and antifertility agent. Therefore, this chapter is intended to give a general overview on the bioactive constituents and the secondary metabolites of *Buchholzia coriacea* Engl. and the pharmacological benefits attributed to the plant. *Buchholzia coriacea* belongs to Capparaceae family.

Oghenesuvwe et al. (2015) claimed that *Buchholzia coriacea* can be used as a valuable substitute for treatment of some diseases such as malaria,

diarrhea, ulcers, rheumatism, asthma, cough, worm infection, hypertension, diabetes, impotence, psychiatric disorders. Several of these has been proven scientifically and validated through ethno-pharmacologically.

84.2 BIOACTIVE CONSTITUENTS

Alum et al. (2018) compared and evaluated the constituents of *B. coriacea* leaves using ethanol, ethyl acetate (EAE) and aqueous portions. The contents of mineral, vitamin as well as phytochemical constituents of the fractions along with extract was determined. The constituents analyzed on the phytochemical at mg/100 g in the samples were in the order: glycosid es<steroids<saponins<tannins<flavonoids<alkaloids<phenols<terpenoids. The lethal dose toxicity revealed that the ethanol extract of the study plant caused no harm to the rats even when the body weight is at 5,000 mg/kg. Moreover, Okolie et al. (2019) carried out an investigation using butanol fraction of *Buchholzia coriacea* on rat for the animal studies to treat Type 2 diabetes the result by a collaboration which links corpulence to β-cell dysfunction along with insulin resistance (IR). It was revealed that Type 2 diabetes by means of streptozotocin (STZ) single dose (40 mg/kg, i.p.), high fructose (20%w/v, p.o.) in rats. *In vivo* antioxidant activities likewise enhanced although histological segments in cured rats appeared to have reduced material harm in kidneys, pancreas, heart as well as liver. Some of the identified compound though GC-MS are stearic, oleic, n-hexadecanoic acids as well as 2-methyl-pyrrolidine-2-carboxylic. The phytochemical constitutes of *Buchholzia coriacea* includes tannins, alkaloids, saponins, anthraquinones, flavonoids, glucosides (Adediwura et al., 2011; Enechi et al., 2011). Ojinnaka et al. (2015) reported that *Buchholzia coriacea* have been revealed to possess many therapeutic values due to the presence of many bioactive agents like cyclooctasulfur, (Z,Z)-9,12-octadecadienoic acid, oleic acid, n-hexadecanoic acid, 5-hydromethylfurfural, methyl ester (Z,Z)-9,12-octadecadienoic acid, 2,3-dihydro-3,5-dihydroxy-6-methyl-4H pyran-4-one, (E)-9-octadecanoic acid, undecane, 1-methyl-pyriolidine-2-carboxylic acid, palmitoleic acid, 2-methyl-pyrrolidine-2-carboxylic acid, beta-sitosterol, methyl ester 3,5-dicyclohexyl-4-hydroxy-benzoic acid, l-[-]-4-hydroxy-1-methylproline and stigmasterol with so many other bioconstituents.

Reports showed that *B. coriacea* contains anthraquinones, alkaloids, saponins, flavonoids, tannins, and cardiac glycosides (Eze et al., 2017).

Buchholzia coriacea seed oil contains oleic, palmitic, stearic, and docosanoic acids as well as ascorbic acid-2,6-dihexadecanoate, 2-methyl-pyrrolidine-2-carboxylic, estra 1,3,5-trien-17βol, and n-hexadecanoic acid (Okolie et al., 2019; Ogechukwu et al., 2016).

84.3 PHARMACOLOGY

Several medicinal attributes of *Buchholzia coriacea* have been established such as larvicidal effect (Adediwura et al., 2011), anthelminthic activity (Nweze and Asuzu, 2009; Adediwura et al., 2011), antiplasmodial activity (agents that suppresses muscle spasm) (Okoli et al., 2010), analgesic activity (Ezeja et al., 2011), antibacterial activity (Mbata et al., 2009), and anti-diarrheic properties (Anowi et al., 2012),

84.3.1 LARVICIDAL EFFECT

Adediwura et al. (2011) reported that *Buchholzia coriacea* has larvicidal effect. In their study, different solvent extraction process such as Petroleum ether, methanol, and chloroform fractions extract of *B. coriacea* seed were utilized to investigate the antimalarial effects due to their larvicidal effect against *Anopheles gambiae* at different doses. The authors showed that the extract significantly increased the mortality rates of the *Anopheles gambiae* larva thereby proving to be an effective agent against malarial parasites.

84.3.2 IMMUNOMODULATORS AND ANTIOXIDANTS

Eze et al. (2017) reported that *B. coriacea* contains anthraquinones, alkaloids, saponins, flavonoids, tannins, and cardiac glycosides. *Buchholzia coriacea* seed oil contains oleic, palmitic, stearic, and docosanoic acids as well as ascorbic acid-2,6-dihexadecanoate, 2-methyl-pyrrolidine-2-carboxylic, estra 1,3,5-trien-17βol, and n-hexadecanoic acid. Many of these phytochemicals are shown to possess immunomodulatory and antioxidant properties against *Trypanosoma brucei* and other bacterial infections. The phytochemicals can boost the immune response and cause immunostimulatory activity in an infectious microenvironment.

84.3.3 ANTHELMINTHIC ACTIVITY

Nweze and Asuzu (2009) and Adediwura et al. (2011) reported that helminths are an infection with nematodes, particularly in the gastrointestinal organs resulting into low productivity and intestinal disorders. The authors demonstrated anthelmintic effect of *Buchholzia coriacea* seeds.

84.3.4 ANTIPYRETIC EFFECTS

Epa et al. (2019) reported that stem bark of *B. coriacea* ethanol extract displayed antipyretic activities utilizing Brewers' yeast induced pyrexia and suggested that these effects thus justified the traditional use of the stem barks of *Buchholzia coriecea* in fever and pain treatment. This could be linked with availability of bioactive compounds like saponosides, tannins, flavonoids, sterols, anthocyanins, and terpenoids (Epa et al., 2015). Studies have indicated that medicinal plants especially *Buchholzia coriacea* play a critical role against different animal and human diseases. Oghenesuvwe et al. (2015) reported the antipyretic effects of *Buchhoizia coriacea* (Wonderful Kola) and attributed the effects due to the presence of essential chemicals such as flavone glycoside, phlobatannins, proteins, carbohydrates, tannins, alkaloids, flavonoids, saponins.

Odukanmi et al. (2019) reported that *Buchholzia coriacea* extract modified electrolyte compositions and salivary secretion as antipyretic mechanisms due to the earlier report that there is reduced secretion of saliva in malarial patients. The high chloride ion and bicarbonate of *Buchholzia coriacea* in the treatment of fever and pyrexia with a potent efficacy in combination with palm oil has been reported and proven efficient secretory functions of the ductal acini maintaining the acid-base balance as indicated by the high pH value and possibly systemic acid adjustment. The utilization of the extract of *B. coriacea* in fever and pyrexia treatment with a potent efficacy in combination with palm oil has been reported. Also, certain antimalarial therapy such as hydroxychloroquine can facilitate reduced physiology of salivary glands.

84.3.5 ANTITRYPANOSOMAL ACTIVITY

Many medicinal plants and extracts have shown significant anti-trypanosomal activity due the availability of active ingredient like saponosides, tannins, flavonoids, sterols, anthocyanins, and terpenoids (Nweze et al.,

2011a). Assefa (2017) reported that *Trypanosoma congolense*, a flagellated protozoan causes trypanosomiasis with multidimensional impact on human and treatment has remained challenging due to resistance by the parasites. The anti-trypanosmal activity of *Buchholzia coriacea* was reported by the author to be significantly effective in the cure of this disease. Nweze et al. (2011b) revealed that *Buchholzia coriacea* seed possess anti-trypanosomal, antipyretic, and analgesic that result into fever. These effects are attributed to the presence of β-sitosterol and α-sulfur.

84.3.6 ANALGESIC ACTIVITY

Ezeja and co-authors in 2011 reported the role of *B. coriacea* in analgesic activity of different writhing reflex analgesic models. The authors suggested that the analgesic effect of *Buchhoizia coriacea* may be through peripheral and central pathways mediated by peripheral inhibition of the activities or production of prostaglandins. Pain is seen as a distressing feature of many diseases like pyrexia, physical trauma, and chemical stimulation. The search for newer natural analgesic agents has been documented due to their cheap nature, accessibility, and nontoxicity.

Olaleye et al. (2012) revealed the analgesic and anti-inflammatory potentials of *Bulchholzia* seeds ethanol extract. The authors revealed that serotonin, kinins, and histamine have been associated with inflammatory mechanisms in the early phase of pain while prostaglandins secretion seems to be involved in the second phase of the edema formation. The authors attributed the beneficial role of *Bulchholzia* seeds ethanol extract against inflammation, pain, and fever to the presence of anthraquinones, saponins, tannins, cardiac glycosides, alkaloids, flavonoids, and reducing sugars.

84.3.7 ANTIPLASMODIAL ACTIVITY

Studies have shown that malaria remains the leading cause of public health challenges in many parts of the sub–Saharan African due to the increased drug-resistant of *Plasmodium falciparum* strains. Thus, the search for an effective natural biomolecule derived from plants has increased tremendously in the last few decades. Many of the phytochemical molecules in *Bulchholzia* seeds ethanol extract was reported to be effective in malaria fever treatment. These phytochemicals are alkaloids, simple sugars, saponins, terpenes, flavonoids, essential oils (EOs), xanthenes, stilbenes, xanthones,

strychnines, labdanes, sungucine derivatives, amino acid derivatives, quassinoids, and anthraquinones.

Enechi et al. (2016) reported the role of *Buchholzia coriacea* on hematological changes and hepatic physiology in *Plasmodium berghei*-infected Mice. The authors noted that *B. coriacea* seed extract significantly suppressed parasitemia and repairs altered hematological parameters in mice infected with malaria parasite. Also, the extract was able to improve the hepatic function altered in mice infected with malaria parasite. These effects were alluded to the presence of bioactive chemicals such as saponin, flavonoids, essential oil like Di-n-butyl phthalate and tannins. Eze et al. (2017) reported that *Buchholzia coriacea* seed extract induced Immunomodulatory activity against *Trypanosoma brucei* due to the presence of alkaloids, cardiac glucosides, anthraquinones, flavonoids, saponins, tannins. The authors thus attributed the larvicidal, anti-plasmodial, anthelminthic, analgesic effects to the bioactive molecules. Okoli et al. (2010) also investigated the anti-plasmodial activity of *Buchholzia coriacea* aqueous extract in mice. The anti-malarial potentials of *Buchholzia coriacea* was reported to be due to the active natural products.

84.3.8 CARDIOVASCULAR EFFECTS

Studies have demonstrated that excess accumulation of free radicals can cause inflammation, increase in blood circulation, swelling, pain, and cardiovascular diseases (Dosso et al., 2020). Anti-inflammatory effects of natural plant like *Bulchholzia coriacea* can help to mitigate against the excess storage of reactive oxygen species (ROS). *Bulchholzia coriacea* is rich polyphenolic compounds like as flavonoids, phenols, tannins, quercetin, myricetin, and flavone capable of preventing tissue damage and degeneration (Charles et al., 2015). Many reports have showed that those tissue products which generate inflammatory response are histamine causing elevated tissue permeability, constriction of the bronchioles, contraction of smooth muscle, lipid mediators such as prostaglandins, platelet-activator factor, lipoxins, and leukotrienes, serotonin, bradykinin, complement system products, blood clotting system products, compounds released by the sensitized lymphocytes like lymphokines which are collectively referred to as autocoids, known messengers of inflammatory reactions (Eze et al., 2019).

Olaiya and Omolekan (2013) revealed that *Buchholzia coriacea* induced Anti-hypercholesterolemic activity thus reducing the detrimental effects of

hypercholesterolemia on the cardiovascular system such as atherosclerosis, ventricular hypertrophy, and hypertension. The authors attributed these effects to the high concentration of bioactive ingredients such as lupeol, terpenes, oleic, 2-methyl-pyrrolidine-2-carboxylic, stearic, steroids, n-hexadecanoic acid, flavonoid with different biological properties.

84.3.9 NEUROLOGICAL EFFECTS

Onasanwo et al. (2013) reported that *Buchholzia coriacea* possess many phytochemicals with neuro-active metabolites and neuro-behavioral activity. Experimentally, authors investigated the role of *Buchholzia coriacea* neuro-pharmacological potentials utilizing different test models. From their studies, it was discovered that *Buchholzia coriacea* displayed stronger antidepressant, anxiolytic, and analgesic activity with increase in dose in comparison with diazepam. The authors revealed that the plant possesses stabilizing role on the motor activity in the brain.

The pain signals are transmitted through the unmyelinated C fibers and myelinated A delta (Aδ) to the spinal cord via the dorsal horn synapses. Calixto et al. (2000) revealed that many medicinal plants present a crucial source of new agents with active pharmacological activity against pain and inflammation in the brain. Many of these plant molecules are safe and effective therapeutic agents against many ailments induced by pain, inflammation, and oxidative stress. Many herbs are endowed with anti-inflammatory and analgesic potentials as a result of different phyto-compounds. An example of these plants is the *Buchholzia coriacea* with great neuro-pharmacological potentials.

Calixto et al. (2000) revealed that tannins, steroidal compounds, flavonoids, and alkaloids may be responsible for analgesic activities. Terpenoids are linked to antinociceptive activity via inhibition of thrombocyte aggregation, thus interfering with signal transduction mechanisms of pain. Studies have demonstrated that Saponins are associated with analgesic activities through modulating the NMDA, GABAA, non-NMDA receptors for brain nociception a non-opioid mediated property via stimulation of descending serotonin and α2-adrenergic pathways.

Abayomi et al. (2019) reported the brain-protective effects of *B. coriacea* seed against sodium azide toxicity in the brain. In their study, it was reported that *B. coriacea* treatment was able to boost the antioxidant defense mechanisms in prefrontal cortex. The authors revealed that sodium azide toxicity

in the brain is responsible for many neurodegenerative diseases as a result of activating intrinsic mitochondrial apoptotic pathway resulting in activation of caspase-9 by controlling cytochrome c release in the mitochondrial intermembrane space. The neuroprotective effects of *Buchholzia coriacea* seed was as a result of high bioactive molecules availability like saponins, phenolic compounds, alkaloids, tannins, and flavonoids.

84.3.10 ANTI-ULCEROGENIC EFFECTS

The anti-ulcerogenic effect of *B. coriacea* has been reported. In a study, *B. coriacea* seed ethanol extract ameliorated gastric mucosa of ulcer-induced rats in comparison with controls. This is attributed to the phytochemicals including tannins and flavonoids. Tannins are able to precipitate microproteins at ulcer sites, hence, protecting the gastric mucosa from the effects of the proteolytic enzymes (Enenchi and Nwodo, 2014). The anti-ulcer effects of *B. coriacea* could also be associated with the significant presence of flavonoids which opposes histamine effects. *B. coriacea* extract inhibited gastric acid secretion and contractile responses induced by histamine (Enenchi and Nwodo, 2014; Oghenesuvwe et al., 2015).

Owonikoko and coworkers have reported that the anti-ulcerogenic action of *B. coriacea* against acetic acid-induced ulcer to be mediated through decreased lipid peroxidation (LPO) suggesting that the *B. coriacea* possess free radical scavenging ability. Therefore, the ulcer healing effect of *B. coriacea* may be via decreased free radical generation (Owonikoko et al., 2015). In addition, Salami, and colleagues also reported that dietary supplementation of *B. coriacea* seeds have a gastro-protective effect against ischemia reperfusion-induced gastric ulceration (Salami et al., 2017).

84.3.11 ANTI-INFLAMMATORY EFFECTS

The ethanol extract of *B. coriacea* seed inhibited prostaglandin and significantly reduced carrageenan-induced edema 3 hours post carrageenan injection at 200 mg/kg (Olaleye et al., 2012). Furthermore, *B. coriacea* seed extract reduced the formation of granulomatous tissue, an indication of inhibition of sub-chronic inflammation (Olaleye et al., 2012).

B. coriacea suppressed colon weight induced by acetic acid, thus, indicating the inhibitory ability of *B. coriacea* on the influx of neutrophils and macrophages to injury site (Omayone et al., 2018). Neutrophil infiltration

characterizes ulcerative colitis. *B. coriacea* enhanced serum glutathione (GSH) reductase and catalase (CAT) as well as inhibited the production of malondialdehyde (MDA) levels (Omayone et al., 2018). In prostatic, epididymal, and seminal vesicle inflammation, ME of *B. coriacea* seed has been considerably reported to reduce reproductive organ (Oghenesuvwe et al., 2015).

84.3.12 ANTI-DIARRHEAL PROPERTIES

B. coriacea was also reported to possess anti-diarrheal properties. This is attributed to the presence of tannins which produce protein tannates via protein denaturation, thereby enhancing intestinal mucosa resistance which reduced diarrhea, due to synergistic effects of phytochemicals in *B. coriacea* (Anowi et al., 2012).

84.3.13 ANTIOXIDANT EFFECT

Studies have shown that *Buchholzia coriacea* contains phenols, flavonoids which are capable of acting as antioxidants against free radicals responsible for many ailments in the body (Fakoya and Olusola, 2019). The ethanol extract of *B. coriacea* seeds antioxidant effect has been reported (Enenchi and Nwodo, 2014). The presence of flavonoids in *B. coriacea* is also the basis of anti-oxidative effects of *B. coriacea.*

84.3.14 ANTIMICROBIAL ACTIVITIES

Mbata et al. (2009) revealed that *Bucholzia coriacea* extract displayed significant antimicrobial effects against *Escherichia coli, Salmonella typhimurium, Staphylococcus aureus, Vibrio cholerae,* and *Bacillus cereus.* The authors reported that the antimicrobial effects were due to the presence of alkaloids, carbohydrates, anthraquinones, cardiac glycosides, glycosides, resins, flavonoids, saponin, steroidal terpenes, tannins, and steroidal rings. Ibrahim and Fagbohun (2013), during their study found out that when extract concentration was elevated there was improved antibacterial potency upon the application of ME of *B. coriacea*. Then they found out that *A. niger* was more susceptible compared to *Rhizopus* sp. and *T. virida*. Ibrahim and Fagbohun (2013) recorded in their research that *Bucholzia coriacea* extract

inhibited the proliferation of the organisms they worked on at different concentrations. They attributed the antimicrobial efficacy of the plant extract to the phytoconstituents inherent in the *Bucholzia coriacea* (Ibrahim and Fagbohun, 2013; Ajaiyeoba et al., 2001).

These secondary metabolites typically disrupted the proliferation, and the metabolic action that pathogenic organisms would have unleashed. Their study disclosed the great effect of ME from *B. coriacea*, which they said was as a result of higher concentration of the extract showing wider zone of inhibition better than ethanol extract. This was ascribed to the polarity of the solvents, the more a solvent is polar, the better the extraction yield (Chang et al., 1997). Moreover, when the concentration of extract was increased it gave an increased antimicrobial activity resulting in a wider zone of inhibition. *Staphylococcus aureus* was found to be most susceptible with the wider zones of inhibition followed by *Salmonella typhimurium* and *P. vulgaris*. They claimed that the antibacterial activity of the *Bucholzia coriacea* might be taken into consideration and utilization as an antimicrobial agent widely acceptable in combating a lot of diseases (Ezekiel and Onyeoziri, 2009). The varying levels of susceptibility of the microorganism could be a resultant effect of the inherent forbearance of the microorganisms to environ and the addition of phyto-chemicals in the extracts. The bacteria strain they used in the research was obtained from different clinical sources then they concluded that the plant extracts could be used to manage diverse health crises.

Numerous scientists have worked on the antifungal activity of *B. coriacea* on several fungi strains using the plant extract (Bokhari, 2009). Bokhari (2009) found that of *B. coriacea* hexane and methanol fractions inhibited the proliferation of *A. niger* and *Trichoderm viride*.

The presence of some phytochemicals in was affirmed for its antimicrobial potency in the work of Ajaiyeoba et al. (2001). Moreover, Ajaiyeoba et al. (2003), also, reported that there was an increased antimicrobial efficacy when there was an increase in concentration of the plant extracts. There was conclusion that, the presence of some phytochemicals inherent in *B. coriacea* has promising potentials being used as new complex of antimicrobial drugs.

84.3.15 ANTI-DIABETIC EFFECT

Locally, *B. coriacea* seeds are used in the management of hypertension, cold, diabetes, and rheumatism. However, Adisa, and coworkers demonstrated the anti-diabetic effect of *B. coriacea* in experimentally induced diabetes. In

this study, Adisa, and colleagues demonstrated that *B. coriacea* seeds have hypoglycemic potential especially in diabetic rats. Consequently, observed hypoglycemic potential of *B. coriacea* extract may be due to its ability to enhance insulin sensitivity via repairs of necrotic β-cells of the pancreas (Adisa et al., 2011).

Furthermore, diabetes has been associated with nephrotoxicity, cardiotoxicity, and hepatoxicity. Elevated AST and ALT signified loss of cell membrane integrity, however, *B. coriacea* treatment lowered the elevated AST and ALT circulating levels showing conserved hepatic cell membrane integrity (Adisa et al., 2011). In the same vein, Adisa, and colleagues revealed that *B. coriacea* possess nephron-protective activity by lowering circulating creatinine and urea levels that were elevated in the diabetic rats (Adisa et al., 2011). Hence, *B. coriacea* have ability to ameliorate diabetes-induced renal injury.

Interestingly, alongside the hypoglycemic effect demonstrated by *B. coriacea*, Adisa, and coworkers also revealed that *B. coriacea* ameliorate dyslipidemia indicated by decreased circulating triglyceride and total cholesterol (TC) that were elevated in diabetic rats (Adisa et al., 2011). Essentially, this effect may be through its ability to inhibit to hormone sensitive lipase resulting reduce lipolysis and decreased conversion of triglyceride into free fatty acids and cholesterol (Mir et al., 2008).

Gbagbeke et al. (2018) revealed that *B. coriacea* aqueous and ethanol extract reduced glucose level in experimental diabetic rats at a dose of 250 mg/kg aqueous. The glucose lowering effect was found to be both dose-sensitive and duration dependent in rats. Administration of ethanol and butanol fractions of the plant resulted in attenuated fasting blood glucose and lowered TC and triglyceride in diabetic rats (Adisa et al., 2011). Reduction in hepatic lesion together with decreased liver enzyme was also observed. Administrations of 150 mg/kg, 300 mg/kg, and 600 mg/kg body weight doses orchestrated a dose-related decrement in fasting blood glucose in diabetic rats according to the work of Nwaehujor et al. (2012). There was also a change in lipid profile such as a decline in TC and triglyceride. An experimental model of diabetes mellitus (DM) induced by Okolie et al. (2019) was investigated for possible amelioration using butanol fraction of the extract at 20, 200, and 400 mg kg^{-1} body weight or combination of the extract and glibenclamide. Following two weeks of treatment, either butanol extract or combination of butanol extract and glibenclamide instituted a reversion in elevated fasting blood glucose and abnormal liver and kidney function tests. The butanol

extract also exhibited the strongest antioxidant capacity and greatest inhibitory effect on alpha-amylase *in vitro*.

Fakoya (2017) investigated the protective potential of alcoholic and aqueous extracts of the plants against arsenite-induced hepatocellular damage at doses of 100, 200, 300, and 400 mg kg^{-1} body weight. Treatment of rats with extracts doses prior to sodium arsenite-induce challenge resulted in repelled the elevated levels of aspartate transaminase, alanine transaminase, alkaline phosphate, lactate dehydrogenase in the dose-related pattern. Enechi and Nwodo (2014) showed that *Buchholzia coriacea* seed caused a dose-dependently depression in indomethacin-induced gastric mucosa ulceration and histamine-induced gastric acid secretion decreased and prevented histamine-induced contractile effect.

84.3.16 NEPHROPROTECTIVE EFFECT

Ugwu et al. (2018) did a comparative study on nephroprotective significant of aqueous, MEs along with crude seed powder of *B. coriacea* in liver dysfunction rats and was examined for about 56 days. The aqueous and methanol fractions as well as crude powder decreased the amount of uric and creatinine acid significantly and as well reduced slightly throughout the periods of the treatment. The study also showed that there was increased significantly with the TP content. Although, reduction was observed with 200 mg/kg crude powder and aqueous extract one-to-one in urea intensities. Visible nephroprotective significant may be credited to the existence of phytochemicals such as tannins and flavonoids that act as antioxidants.

KEYWORDS

- **analgesic activity**
- **antihelmintic activity**
- **antipyretic effects**
- ***Buchholzia coriacea***
- **larvicidal effect**
- **nephroprotective effect**

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CHAPTER 85

Pharmacology, Phytochemistry, and Medicinal Usefulness of *Basella alba* L.

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85.1 INTRODUCTION

Basella alba L. (Indian spinach) is a plant from the family Basellaceae. It is grown throughout the tropics, and the young leaves are used as cooking vegetables. The original range of *Basella alba* is probably in Southeast Asia. However, it is common as a cultivated plant throughout the tropics. *Basella alba* is a neophyte in tropical Africa and Asia, China and Taiwan, New Guinea, South America, Panama, the Caribbean islands, and islands in the Pacific. *Basella alba* is globally planted; in calm season, it exhibits a climbing type of growth. It is characterized by fleshy water tissues which serve as the plants water reservoirs with numerous meters long. Other names for *Basella alba* are Malabar spinach, lalbachlu, Valchibaji, Alugbati, Poi, Amunututu. *Basella alba* is grown as a perennial vegetable in tropical zones and propagation takes place by cuttings or seeds. The young, leafy shoots are harvested six months after planting. The leafy shoot tips are prepared as cooking vegetables in a similar way to spinach. The fleshy leaves have a high nutritional value, and they contain 5% carbohydrates, 5% protein, 0.7% fat, calcium, phosphorus, iron, provitamin A and vitamin C (Anusuya et al., 2012).

85.2 BIOACTIVE CONSTITUENTS IN *BASELLA ALBA*

Several researchers have documented numerous compounds that could be isolated from *Basella alba*. Some of these compounds include acacetin, arginine, basella saponins A to D, β-carotene, betacyanin, rutin, ferulic acid, gomphrenon I, II, III, gomphretin I, betadin dihexose and isobetadin-dihexose, isoleucine, leucine, lupenol, monordin IIB, IIC, niacin, syringic acid, threonine, vanilla, vitamin C, E, and K (Khare, 2007; Lin et al., 2010; Kamar et al., 2013; Toshiyuki et al., 2001; Anusuya et al., 2012).

Basella alba is a crucial vegetable which could be green or red purple at the base when fully matured. Gupta and Prakash (2009) reported the effectiveness in the utilization of Basella as a food product and as a medical product. The study of Karam et al. (2016) assessed some dietary fibers in Basella like minerals, vitamins, and essential amino acids; bioactive metabolites like tannins, sterols, carotenoids, flavonoids, phenols, among others.

In 2008, Yang et al. revealed the presences of vitamin A, C, K, E, folic acid, niacin, riboflavin, thiamin, proteins, fats, and minerals such as magnesium, iron, and calcium in *Basella alba.* Some phytochemicals were also found like flavonoid (Yang et al., 2008; Khare, 2007). Upon partial purification of *Basella alba*, D-galactose containing polysaccharide was found to be the most abundant complex present. *Basella alba* was found to contain a unique saponins known as basella saponins, several amino acids, phenolic compounds, betalain pigment, its mucilage also comprises of complexes of polysaccharides and glucan (Haq et al., 1969; Toshiyuki et al., 2001; Khare, 2007; Maisuthisakul and Ritthiruangde, 2008).

In the findings of Deshmukh and Gaikwad (2014) they observed that, *Basella alba* is rich in ascorbate and vitamin A, saponins, flavonoids, numerous amino acids, carotenoids alongside organic acids. Numerous *in vitro* along with *in vivo* investigations showed that plants can also be enhanced with active principles/substances for therapeutic prospects. Main biological activities and therapeutic potentials documented for *B. alba* include antidiabetic, androgenic, antimicrobial, antiulcer, antioxidant, CNS depressant, anti-inflammatory, antiviral, wound healing as well as hepatoprotective benefits. *B. alba* is also used for the cure of skin diseases, digestive disorders, pimples, bleeding piles, irritation, urticaria, whooping cough, anemia, aphthae, leprosy, malignant growth, insomnia, burns, gonorrhea, ulcers, headache, liver disorders, diarrhea, sexual asthenia as well as bilious vomiting. Shankul et al. (2013) in their work reported that *Basella alba* has some essential minerals such as iron, calcium, vitamin C as well as vitamin A.

Adhikari et al. (2012) noted that several portions of the plant are utilized for cure of the ailments along with diverse therapeutic activities of animal and most importantly human being throughout the world particularly in the places like China and India. A lot of people have been using it to treat rubefacient, catarrh as well as aperient contagions. Some compounds isolated are kaempferol, basella saponins and betalin.

However, in the recent time, Bamidele et al. (2020) examined that the increasing utilization of the plant is due to the various bioactive compounds present which are responsible for its therapeutic potential. They examined the significant effect on ME of *B. alba* leaves on stress reduction in rats. However, it was practically shown that, the stressed rats, revealed an increase by the means of fasting blood glucose along with white blood cell count, even though there were significant reductions in glutathione (GSH) concentration and superoxide dismutase (SOD) activity once related to other study (Palanuvej et al., 2009).

Basella alba is a natural product with little or no toxic effect and very cost effective (Malviya et al., 2011). Gums and mucilage obtained from *Basella alba* have properties that make it of great use in the pharmaceutical industries (Evans, 2001). It contains galactose, arabinose, rhamnose, which forms larger molecular aggregate in solution. *Basella alba* has wide range of usage, such as emulsifiers, gel, thickening agent, stabilizer, and film forming agent, it could also confirm cytoprotective effect on human in treating ulcer (Chowdhury et al., 2017, 2018). The mucilage of *Basella alba* has been utilized as an additive which improves the effectiveness of medicinal intervention (Chatchawel et al., 2010).

85.3 ETHNOBOTANICAL AND TRADITIONAL USES

Basella alba have long been used in ancient times. Presently scientists have brought about different means in which active components from the leaves have been experimented and found useful as ethnomedicinal product and as therapeutic material. This plant has been used to alleviate certain health conditions. Regular intake of *Basella alba* was found to improve human body vitamin A (Haskell et al., 2004). Indigenes in some rural parts of India make paste from the root of the red type of *Basella alba* alongside with rice water for stomach wash, in treating fluctuating menstrual periods. Some parts of Nigeria were found using fresh leaves of *Basella alba* as analgesic agent, androgenic agent, anticonvulsant, and anti-inflammatory agent and in treating anemia. The paste from the root is usually applied to reduce

swelling and pains from burns. It is used against skin disease usually by sexual workers and as laxatives in infants. Its juice is used to lessen labor pain in pregnant women, also in treating dysentery and diarrhea. The fruits of *Basella alba* were used as black colorant for food (Anandarajagopal et al., 2011; Pati, 2010). It is used as an antipyretic in India (Saikia et al., 2006). It is also being found to be useful as an anticancer agent against leukemia and melanoma (Balachandran and Govindarjan, 2005), mixture of both root and leaves has been used to reduce stomachache after giving birth and in increasing breast milk production in breast feeding mothers (Chifunderk et al., 1998). The Nepali people use *Basella alba* as soup thickening agent (Ramu et al., 2011), upon maceration of *Basella alba* leaves the juice is used to cure the problem of infertility, frequent abortions, painful labor and pelvic inflammatory diseases. The leaves are often used to reduce constipation and gastrointestinal disorder and in headache treatment (Yasmin et al., 2009; Jadhav, 2011).

Kirtikar and Basu (1975) gave a report about India's use of *Basella alba* in veterinary and also for treating gonorrhea and balanitis. Palada and Crossman (1999) reported the use of *Basella alba* in Buea and Cameron to reinforce contraction in pregnancy and facilitate easy delivery. In Nigeria, report revealed that *Basella alba* is used as analgesic, antifungal agent, anti-convulsant, androgenic agent and in treating anemia (Bamidele et al., 2010; Premakumari et al., 2010; Anandarajjagopal et al., 2011). *Basella alba* is also used to lessen digestion disorder. The sap from the plant is used in anointing areas of the body affected by acne (Rathee et al., 2010). Rahmatullah et al. (2011) reported the use of *Basella alba* as an anticancer agent, to alleviate stomachache, as insecticide, to stop bleeding. *B. alba* whole plant is also used to stimulate weight of underweight adults or children. Mohammed et al. (2012) reported Nigeria use of the whole plant to enhance fertility and wound gotten from burns.

85.4 PHARMACOLOGICAL USES

Studies have revealed medicinal importance of *Basella alba* such as antioxidant, anti-inflammatory among others (Nirmala et al., 2010; Kachchhaua, 2006; Anandarajapogol et al., 2011; Bamidele et al., 2014). Product of gel-like substance from *Basella alba* exhibited great substance which could later be developed into cosmetics and medicine in treating skin infection.

Sheela and co-authors in 2004 analyzed the macronutrients available in Basella and then quantified the presence of carbohydrate, energy, fiber,

moisture, and protein. Toshiyuki et al. (2001) stated that *Basella alba* contains basella saponins while, Maisuthisakul et al. (2008) added that peptide and phenolic complexes were found in the plant. Olajire and Azeez in 2011 revealed that *B. alba* contains flavonoids, ascorbic acid and DPPH antioxidant activity. Khare (2007) found the *B. alba* leaves to possess carotenoids, polysaccharides that are soluble in the presences of water and vitamin K. Several bioactive components were found in *Basella alba* (Khare, 2007; Glassgen et al., 1993; Hebbar et al., 2004).

85.5 PHARMACOLOGY

85.5.1 ANTIPYRETIC EFFECTS

Bamidele et al. (2020) analyzed the role of *Basella alba* leaves on stress and discovered that the plant significantly increased the antioxidant enzymes with an increase in dose, thus ameliorating the adverse effects like the generation of free radicals caused by stress. Saikia et al. (2006) assessed the analgesic, anti-fungal, and anti-inflammatory effects of *Basella alba*. In 2012, Adhikari et al. documented that *B. alba* extract was utilized for analgesic, antipyretic, and anti-inflammatory activities, particularly the leaves and stem. Das et al. (2019) claimed that the extract of *Basella alba* exhibit anti-pyretic effects which could be attributed to the presence of anthocyanin. Chandrasekar et al. (2015) reported the role of *Basella alba* on pyrexia. They revealed that the plant displayed strong antipyretic activity as compared with paracetamol. These effects can be attributed to the presence of active biomolecules such as saponins, betalain, kaempferol, carotenoids, quinines, simple phenolic glycosides, betacyanidin, and gomphrenins.

85.5.2 CARDIOVASCULAR EFFECTS

Gunasekaran et al. (2015) reported the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase suppressive role of *Basella alba*, including the utilization against hypercholesterolemia. The authors revealed that this enzyme is important in the mevalonate pathway during the generation of cholesterol. The blockage of this enzyme will significantly suppress the production of cholesterol in the liver. Over the years, many synthetic drugs are utilized for the management of cholesterol, but recently, many studies have revealed that natural bioactive molecules are currently

being utilized for the inhibition of HMGCoA reductase. *Basella alba* leaf extract has been revealed by the authors to fall under this category with very potent anti-HMG-CoA reductase activity. The hypocholesterolemia and cardiovascular effects have been alluded to the presence of bioactive chemicals like phenol 2,6-bis(1,1-dimethylethyl), eicosyl ester, oleic acid, naringin, 1-heptatriacotanol, luteolin, apigenin, α-tocopherol and ascorbic acid.

Gunasekaran et al. (2015) also noted that *Basella alba* leaves extract contains apigenin, naringin, 1-heptatriacotanol, eicosyl ester, oleic acid, phenol 2,6-bis[1,1-dimethylethyl], with luteolin bioactive molecules which act as vaso-protective, hypercholesterolemia, and cardioprotective function. Urmila et al. (2014) reported that hyperlipidemia is linked to the development of many cardiometabolic dysfunctions, such as atherosclerosis, cardiac failure, and eventually death. They showed that *Basella alba* significantly reversed all the high-risk factors for coronary artery disease, like cholesterol, phospholipids, and triglycerides. The authors attributed these cardiovascular properties like vaso-protective action to the availability of bioactive metabolites like flavonoids, tannins, phenols, gomphrenin, anthocyanin pigments, β carotene, carbohydrates, kaempferol, saponins, and betalin. Studies have demonstrated that the buildup of excess oxidized LDL results into atherosclerotic plaque development that could cause stroke, cardiovascular diseases, and myocardial infarction. In 2015, Gunasekaran et al. documented that *Basella alba* extract caused beneficial role through reduction in the level of triglyceride, total cholesterol (TC), with LDL compared with simvastatin. Thus, *Basella alba* treatment groups showed the desirable effects against hypercholesterolemic and atherosclerotic plague.

85.5.3 NEUROLOGICAL EFFECTS

Recently, Bamidele et al. (2020) revealed that importance of *Basella alba* extract like antioxidant, central nervous effects, and anti-inflammatory. This plant caused antidepressant activity in the CNS on different behavioral tests conducted by the authors.

Moussa et al. (2018) revealed the phytochemical analysis of *Basella alba* and showed that the plant contains polyphenols, tannins, flavonoids, saponins, betalain, steroids, terpenoids, and leucoanthocyanes. In their study, they demonstrated that edible plant consumption for the prevention of many neurodegenerative diseases has gained tremendous recognition recently. This is caused by their accessibility, cheapness, and nontoxic effects. Several

neurodegenerative diseases have been linked to oxidative stress like diabetes, Alzheimer's disease, rheumatism, cardiovascular diseases, and Parkinson's. Also, the central nervous system (CNS) depressant activity of *Basella alba* was also reported by Adhikari et al. (2012) and Deshmukh and Gaikwad (2014). The crucial role of inflammation in many disease conditions like cardiovascular diseases, autoimmune disorders, infection, neurodegenerative conditions, and cancer is becoming acceptable. Again, Anandrajagopal et al. (2011) investigated the central nervous role of *Basella alba* aerial parts and found out that the ME displayed depressant like activity in the nervous system, thus alluded these functions to the presence of some psychoactive compounds such as terpenoids.

Muscle relaxant has been investigated to be influenced by *Basella alba* through antidepressant activity caused by the availability of many active biomolecules like tannin, alkaloid, saponin, terpenoid, glycoside, lutein, ß carotene, zea-xanthin, phenolic compounds, and flavonoid (Abhinayani et al., 2016). There are many physiological responses associated with depression and muscle relaxation such as changes the neurotransmitter levels like norepi-nephrine, dopamine, and serotonin in the brain and skeletal muscle.

85.5.4 ANTI-PROLIFERATIVE/ANTICANCER EFFECTS

Extracts from *Basella* species were found to be cytotoxic to A431, Hep G2 and MG63 cancer cells at a lower concentration, with extracts from *Basella alba* being more effective. Furthermore, other compounds including gallic, salicylic, ferulic, and cinnamic acids also enhance the anti-neoplastc effects of *Basella alba* (Kumar et al., 2018). Angiogenesis is a major step in carcinogenesis; therefore, therapies that target its inhibition could help in properly managing cancer growth. The anti-angiogenic effect of *Basella alba* was also reported by Kumar et al. (2018). In an attempt to test the anticancer potentials of *B. alba* leaves and stem extracts on Ehrlich's ascites carcinoma (EAC) cells, *Basella alba* extracts were seen to inhibit EAC cell growth by inducing mitochondrial apoptosis. This was indicated by the activation of p53 mRNA and inhibition of Bcl-2 mRNA (Islam et al., 2018).

The anti-neoplastic effects of *Basella alba* can also be due to the presence of glucosinolates and myrosinase which are known for their anticancer properties. Isothiocyanates are broken down products of glucosinolates with the ability of detoxifying carcinogens (Garza et al., 2019). There are also evidences that glucosinolates induce glucoronosyl transferase and GSH

S-transferase, thereby protecting against oxidative stress as well as the alteration of steroid hormone metabolism. There are reports that isothiocyanates are involved in mercapturate pathway in some cells of cancer, in which, caspase dependent pathways become activated upon the depletion of GSH.

Furthermore, elevation of S-thiocarbamoyl products enhances the expression of tumor suppressor genes, these processes result in cancer cell death (Garza et al., 2019). The plausible cytotoxic effects of *Basella alba* extract are via the alteration of the permeability of carcinogens via the membranes as well as by binding of phenolic compounds with the transporters of cell membranes (Adhikari et al., 2012). Reports showed significant anti-proliferation of cervical, liver, and breast tumor cells (Kumar et al., 2015; Garza et al., 2019).

85.5.5 ANTI-OXIDATIVE EFFECTS

Oxidative stress, a state of disequilibrium of pro and antioxidants usually with higher pro-oxidant generation has been linked to the pathogenesis of a numerous of diseases. Medicinal plants are good sources of antioxidants which are required for disease prevention and therapy. The antioxidant effect of *Basella alba* has also been reported (Deshmukh and Gaikwad, 2014). *Basella alba* fruit supplied betacyanin which was documented to possess antioxidant properties (Kumar et al., 2013). Elevated ferric reducing antioxidant power as well as serum activity of SOD was observed in laboratory animals to which aqueous extract of *Basella alba* was administered (Arokoyo et al., 2018b). Antioxidant activity of *Basella alba* was also evaluated using hydroxide and superoxide, 1,1-diphenyl 2-picrylhydroxyl, hydrogen peroxide, anti-ferric chloride, hydrogen peroxide system, reducing power in the concentrations of all the listed activities (Reshmi et al., 2012a). Due to the obtained results from this study, they reported that fruits/plants which contain great antioxidant activity could be used as additives in food serving as antioxidant. Gomphretin, I isolated from *Basella alba* suppressed LPS-induced NO production in a dose dependent manner (Lin et al., 2010).

85.5.6 WOUND HEALING PROPERTY

The healing potential of *B. alba* was assayed on male rats by creating bruises on rats back and then treated with *B. alba* extract in the presence of glycerin for three weeks. After weeks of administration, they discovered great healing

activity with aqueous extract of *Basella alba* and complete closure of the wound spot (Mohammed et al., 2012).

85.5.7 ANTIMICROBIAL POTENTIAL

The MEs of *Basella alba* have exhibited marked antimicrobial potency on some gram-positive and gram-negative bacterial strains like *S. aureus*, *Bacillus species, E. coli,* and *K. pneumoniae* and also fungi. *B. alba* exhibited great suppressive potency against *A. niger* during the work of Premakumari et al. (2010). Aqueous extract of *B. alba* also has noteworthy activity against bacteria in different ranges of the tested bacterial strains. *B. alba* is an essential herbal plant in ethno-veterinary for afterbirth treatment and anaplasmosis. The mucilaginous solution obtained from *B. alba* leaves is usually utilized as a popular remedy for constant headaches (Sushila et al., 2010).

The assessment of the antimicrobial potency of the plant showed that the plant exhibited a minimum inhibitory concentration (MIC) at 25 mg ml^{-1} to *Aspergillus niger*, *Bacillus subtilus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Lactobacillus*, *Escherichia coli*, and *Aspergillus fumigatus* and a significant inhibition to *Lactobacillus* spp, *Aspergillus fumigatus* (Reshmi et al., 2012b). Kumar et al. (2018) investigated *in vitro* inhibitory activity of crude chloroform and ethanol extract of various parts of the plants on microbial growth. They discovered that the seeds of the plant exhibited maximum inhibitory zone (40 mm) against *Streptomyces* spp. and minimum inhibition (10 mm) against *Bacillus* spp.

Oyewole and Kalejaiye (2012) utilize agar cup method to ascertain the antimicrobial effect of *Basella alba* against *S. areus, E. coli, C. albicans* and *P. aeruginosa.* The results obtained revealed maximum inhibitory effects on all tested isolates except *C. albicans* at varying concentrations (Sushila et al., 2010).

85.5.8 ANTI-INFLAMMATORY EFFECT

Reports have shown the anti-inflammatory effects of *Basella alba* (Krishna, 2012; Rodda et al., 2012; Deshmukh and Gaikwad, 2014). A comparison of aqueous and MEs of *B. alba* with diclofenac sodium, showed a higher membrane stabilizing effect on human erythrocyte membrane (Vijender et al., 2011). Aqueous extract of *Basella alba* enhanced wound healing in animals as

indicated by the epithelization in lesser number of days (23 days) compared with animals in the solvent control and the untreated groups that epithelized at 35 and 39 days, respectively. This also supports the anti-inflammatory potentials of *Basella alba*. The antidiabetic effect of *Basella alba* extract was assessed and there were significantly reduced serum levels of IL-1β and MCP-1 in animals administered with *Basella alba* extract (Arokoyo et al., 2018a). In another study, *Basella alba* colorant powder down-regulated the mediators of inflammation including interleukin 12, NO, TNF-α, interleukin 1β, prostaglandin E2 (PGE2), and interleukin 6. Furthermore, nuclear factor kappa B (NF-KB) activation cascade was blocked by *Basella alba* (Huang et al., 2016).

Carrageenan and formaldehyde were used while testing the anti-inflammatory potentials of *B. alba* extracts on rats. *Basella alba* aqueous extract was tested at 50 and 100 mg kg^{-1} resulting in lowered inflammation in the rats. For the carrageenan-induced inflammation procedure, they discovered that there was little or no anti-inflammatory activity. Krishna (2012) used pellets from cotton-induced granuloma technique while Rodd et al. (2012) used carrageenan alongside with pellets from cotton-induced granuloma inflammatory techniques in the rats. In both studies phenyl-butazone served as standard. The researchers treated experimented rats via oral suspension of 50% macerated with cold ethanol, the result revealed maximum anti-inflammatory potential. Nantia et al. (2011) also discovered that both methanol and aqueous extracts of *Basella alba* have great anti-inflammatory effects when compared with commercial anti-inflammatory agent such as diclofenac. The authors screened the anti-inflammatory effect of *Basella alba* leaves by inducing the rats with inflammation. And they found that *Basella alba* possess awesome anti-inflammatory activity upon administration.

85.5.9 ANTI-ULCER PROPERTY

Eight weeks old female Wister albino rats were used to assay the antiulcer effects of *Basella alba* with suspended aspirin in 1% carboxyl methyl cellulose (CMC) at 150 mg kg^{-1} to induce ulcer. The results in the studies as parameters altered by aspirin were restored upon treatment with *Basella alba* leaf extract showing antiulcer activity (Venkatalakshmi and Senthamaraiselvi, 2012). Kumar et al. (2012) also discovered the antiulcer effect of *Basella alba* showing that *B. alba* has gastroprotective activity with increased anti-ulcerogenic activity owing to the improved gastric cytoprotective and suppression of secreted acid (Deshpande et al., 2003).

85.5.10 ANDROGENIC POTENTIAL

Studies have revealed the androgenic effectiveness of *Basella alba*, and this was assayed by Moundipa et al. (1999, 2005) using matured male albino rats. They arrived at the conclusion that the weight of essential reproductive features like seminal vesicles, production of testosterone, the activity of prostatic acid phosphate and spermatozoa concentration was greatly increased upon application of both dried and fresh *Basella alba* (Nantia et al., 2011). They found out that extracts of *B. alba* have the strength of stimulating androgen, increase estrogen concentration, could be used in treating male infertility and loss of sexual drive (Nantia et al., 2012).

85.5.11 HEPATOPROTECTIVE EFFECTS

Hepatoprotective role of *B. alba* leaf extract was reported in a study where paracetamol was used to induced liver damage in rats. A dose of 100 mg/kg of *B. alba* aqueous extract demonstrated hepatoprotective potential against paracetamol-induced liver damage by decreasing serum liver biomarkers (bilirubin, serum glutamic pyruvic transaminase (SGPT), proteins, glutamic oxaloacetic transaminase, alkaline phosphatase (ALP)) (Das et al., 2014). Also, histopathological examination revealed that *Basella alba* oral administration reversed degenerative changes in the liver cells and cytoarchitectural alterations were ameliorated by *Basella alba* treatment. Hence, aqueous extract of *Basella alba* demonstrate great liver protective qualities towards liver injury induced with paracetamol (Das et al., 2014).

The Anthocyanin colors found in *Basella alba* have therapeutic benefits such as anticancer, antineoplastic effect, anti-aging effect, it is also used to reduce oxidative stress in pregnant women, it helps to normalize the winding effect of the DNA (Sivasankar et al., 2011). The antmutagenic activity of *Basella alba* was assayed against *S. typhimurium*, the obtained results showed the maximum antimutagenic property. This activity affirms its potential use to protect farm produce. The mechanism by which this is done could be by blocking the mutagen, movement into the cytosol via binding by the phenol to the cell environment (Haskell et al., 2004). There was also alteration in the accessibility of mutagens within the bacteria cell membrane (Phadungkit et al., 2012).

It has been established that *B. alba* aqueous extract by analyzing hematological and biochemical features of Wistar albino rats and it was discovered that there was great elevation in the blood level and a reduction in the activity

of enzyme of the livers. They concluded that introduction of *Basella alba* in every day diet would help to alleviate anemia and help to keep the body in sound health (Bamidele et al., 2010).

85.5.12 ANTIDIABETIC AND ANTIMICROBIAL POTENTIALS

B. alba (Malabar spinach) is a climbing plant found in Africa and Asia and many other countries of the world (Adhikari et al., 2012). The leafy vegetable is eatable and often used in preparing soup. Beyond being a food source, studies have indicated its medicinal might in health and altered health conditions including diabetes mellitus (DM), a disease characterized by abnormal lipid profile and high fasting blood glucose.

Bamidele et al. (2014) revealed that *B. alba* aqueous extract exhibited a high fasting blood glucose-lowering tendency comparable to metformin in experimental diabetic rats when administered at 100 and 200 mg kg^{-1} body weight. In an experiment, diabetes rats orally administered 200 mg/kg body weight for four weeks had suppressed level of the fasting blood glucose associated with experimental DM by orchestrating a decrease in thiobarbituric acid and conjugated diene and an increase in superoxide and serum ferric reducing ability of plasma (FRAP) (Arokoyo et al., 2018b). Other mechanisms underlying the glucose lowering tendency of the plant include reduction in 1L-IB, a pro-inflammatory cytokine and monocyte chemotactic protein (MCP-1), a protein that attracts monocyte to the site of infection (Arokoyo et al., 2018). Stress is linked with elevation in fasting blood glucose. The work of Bamidele et al. (2020) claimed that administration of the *B. alba* extract using methanol as extractant at 60 mg/kg and 120 mg/kg body weight to normal rats decline the fasting blood glucose compared with rats subjected to stress but not healthy control rats.

Concerning the hypolipidemic effect of *Basella alba*, Baskaran et al. (2015b) revealed that administration of 100 mg/kg and 200 mg/kg body weight *B. alba* to hypercholesterolemic rats reduced a rise in low-density lipoprotein, TC, triglyceride through the inhibition of 3-hydroxy 3-methyl glutaryl COA reductase (Baskaran et al., 2015a) responsible cholesterol synthesis endogenously (Adeniyi and Soladoye, 2017).

KEYWORDS

- ***Basella alba***
- **carboxyl methylcellulose**
- **Ehrlich's ascites carcinoma**
- **monocyte chemotactic protein**
- **nuclear factor kappa B**

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CHAPTER 86

Biological Constituents and Medicinal Attributes of *Spondias mombin* L.

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86.1 INTRODUCTION

Spondias mombin L. has been identified as a fructiferous tree that belongs to the family of Anacardiaceae. Most of the parts of the plant are normally utilized for medicinal purposes. *Spondias mombin* has been applied for the treatment of postpartum infections of the uterus most especially in women that have performed an abortion or miscarriage in women (Morton, 1987; Gbile, 1984; Taylor, 2004; Uchendu and Choudhary, 2004).

The leaves segment of *Spondias mombin* has been established to contain the following phytochemical constitutes such as alkaloids, phenols, tannins, alkaloids, flavonoids while the presence of vitamins and minerals such as phosphorus, calcium, sodium, magnesium, potassium have been established to be available in the leaves (Njoku and Akumefula, 2007). *Spondias mombin* is widely distributed in Southern America, coastal areas and rainforest of Africa, West Indies and Asia.

86.2 BIOACTIVES

The leaf extracts contain a series of 6-alkenyl-salicylic acid (Corthout et al., 1994), an anacardic acid derivative that possessed β-lactase inhibitory

activity (Coates et al., 1994); two caffeoyl esters, 2-O caffeoyl- +- allohydroxycitric acid and chlorogenic butyl ester (Corthout et al., 1992). Ellagitannins, geraniin, and galloylgeraniin were reported by Courthout et al. (1991).

Serge et al. (2015) revealed that *Spondias mombin* possess alkaloids, tannins, flavonoids, phenols, vitamins, and saponins. Agbaje et al. (2020) reported the presence of flavonoids, reducing sugar, tannins, cardiac glycosides, terpenes, steroids, alkaloids, saponins, and anthraquinones are active present in *S. mombin.*

Essential oils (EOs) in *S. mombin* principally contains caryophyllene and α-murolene, α-garjunene, δ cadinine and 5-isocedranol (Ayoka et al., 2008). A report showed that the hydro-alcoholic extracts of *S. mombin* leaves contained quercetin, rutin, isoquercetin, chlorogenic acid and ellagic acid (Rey-Blanes et al., 2020). The ME of *Spondias mombin* seed was reported to contain n-hexadecanoic acid, dihydrocapsaicin, tetradecanoic acid, dodecanoic acid, and phenol amidecapsaicin. Hexadecanoic acid has been shown to possess antioxidant and anti-inflammatory properties. Furthermore, dihydrocapsaicin, and capsaicin also possess antioxidant property (Murakami et al., 2001). Hexadecanoic acid–methyl ester, Linoleic acid, 2,3-dihydro-3,5-ddihydroxy-6-methyl and 4-H-pyran-4-one have also been reported to enhance antioxidant effects of *S. mombin* (Abiodun et al., 2020).

86.3 PHARMACOLOGICAL EFFECTS

86.3.1 ANTIPYRETIC EFFECTS

Several studies have reported the inflammation suppressive and antioxidant effects of *S. mombin* extract (Barbara et al., 2016). The plant is revealed to possess many active phytochemicals like phenolic acids, tannins, triterpenes, and flavonoids known to display strong pharmacological activity such as inhibition of COX-2 and cytokines expression, inhibition of NO production, nuclear translocation inhibition and activation of NF-kB. Serge et al. (2015) revealed that *Spondias mombin* possess analgesic activity. They reported that the ME of the plant possesses high levels of alkaloids, tannins, flavonoids, phenols, vitamins, and saponins. The analgesic role of the plant may be through the cyclo-oxygenase pathways, thus blocking the release of prostaglandins, arachidonic acid, and several other pain mediators. Agbaje et al. (2020) reported the antipyretic role of *Spondias mombin*, thus phytochemical analysis was investigated to ascertain the biological active

components available in the plant to determine the molecule responsible for the antipyretic effects. They revealed that flavonoids, reducing sugar, tannins, cardiac glycosides, terpenes, steroids, alkaloids, saponins, and anthraquinones are active present in the plant.

86.3.2 CARDIOPROTECTIVE EFFECTS

In 2011, Iweala and Oludare documented the hypoglycemic role of *S. mombin* and a serious potential in the treatment of diabetes mellitus (DM) which is a major risk factor for cardiovascular disorders. The authors suggested that the cardiovascular properties of this plant are connected to rich phytochemical constituents like tannins, cardiac glycosides, flavonoids, alkaloids, and saponins. Also, the antihypertensive effects and other antioxidant property of *S. mombin* have been established by Iweala and Oludare (2011). Significant inhibition of NO level was reported to cause vasoconstriction resulting in chronically elevated blood pressure–hypertension and other related cardiovascular complications. Thus, high dose of the plant was able to increase NO and ameliorated the effects.

Nkanu et al. (2016) also monitored the hypolipidemic and hypoglycemic effects of *Spondias mombin* leaves extract and demonstrated that the secondary metabolites like alkaloids, tannins, flavanoids, phenolic, and saponins compounds in the plant may be responsible for the strong metabolic effects. It should be noted that hyperlipidemic and hyperglycemic are very high-risk factors for cardiovascular dysfunctions. Nkanu et al. (2016) revealed that *Spondias mombin* possess antagonistic activity against α-Glucosidase and α-Amylase which are an important enzyme in the diabetic pathways. The authors revealed that these effects could be linked with presence of pelandjuaic acid, gallic acid, chlorogenic acid, quercetin, ascorbic acid, nicotinic acid, thiamine, riboflavin, caffeoyl esters, ellagic acid, betulin, coumaroyl, phenolic acid, 6-alkenyl-salicylic acid, anacardic acid and ellagitannins.

86.3.3 NERVOUS EFFECTS

Ayoka et al. (2005) reported the anxiolytic role of *Spondias mombin* against different nervous disorders like psychiatric disorders. From their findings, it was revealed that the plant utilized the $GABA_A$ receptor through GABAergic transmission by opening GABA-stimulated chloride channels or serotonergic pathway to perform its pharmacological activity. It is widely

known that anxiety can be a response due to environmental trigger resulting in psychotic disorders affecting noradrenaline, GABA, BDZ, and serotonin neurotransmitters activities. The central nervous activity could be linked with the presence of anthraquinones, tannins, cardiac glycosides, flavonoids, berberine, naphthoquinones, quassinoids, sesquiterpenes, quinolone, indole, and saponins.

Sonibare and Ayoola (2015) revealed that *Spondias mombin* possesses strong neuromodulatory activity against several neurodegenerative diseases like Alzheimer's, multiple sclerosis, Parkinson's, spongiform encephalopathy and amyotrophic lateral sclerosis through acetylcholinesterase (AChE) inhibitory and neuroprotective activity. The authors claimed that this neuroprotective activity could be alluded to the availability of phyto-constituents in the plant. Ayoka et al. (2006) reported the antiepileptic, sedative, antipsychotic potentials of *S. mombin* leaves extract. They suggested that the plant may be involved in muscarinic, μ-opioid, α2 adrenergic receptor, antidopaminergic activity and GABAergic transmission.

86.3.4 ANTI-INFLAMMATORY EFFECTS

The anti-inflammatory effects of *Spondias* species are documented (Cabral et al., 2016). The dose-dependent anti-inflammatory potentials of *Spondias mombin* extract was indicated by its ability to inhibit paw edema caused by carrageenan. It also reduced lipopolysaccharide (LPS)-induced by TNF-α (Nworu et al., 2011). Additionally, it was reported that *S. mombin* leaf extract could inhibit leucocyte migration to an inflammation site (Cabral et al., 2016).

86.3.5 ANTIOXIDANT EFFECTS

The antioxidant effect of *S. mombin* was attributed to its rich phenolic compounds, particularly chlorogenic and ellagic acids (Cabral et al., 2016). *Spondias mombin* (Tapereba) was reported to be rich in vitamin C and flavonoids including β-cryptoxanthin, zeinoxanthin α and β carotenes. It had a higher antioxidant capacity relative to *Byrsonima crassifolia* (L.) Kunth (Aniceto et al., 2021). Alpha-tocopherol was present in leaf extract (Sabiu et al., 2015). *Spondias mombin* pulp contained elevated levels of potassium, copper, magnesium, and phosphorus (Bailao et al., 2015).

Elevated level of malondialdehyde (MDA) and reduced activity of superoxide dismutase (SOD) suggest lipid peroxidation (LPO) in the gut of the animals to which indomethacin was administered. Aqueous extract of *S. mombin* considerably reduced MDA concentration as well as boosted the activity of SOD (Sabiu et al., 2015).

86.3.6 ANTI-ULCER EFFECT

The gastroprotective effect of *S. mombin* has been reported. In a study, gastric ulcer was induced by indomethacin. This resulted in elevated ulcer index and gastric volume. This could be via mechanisms involving prostaglandin synthesis inhibition or oxidative stress. Administration of *S. mombin* extract ameliorated these effects. There were indications that *S. mombin* extract enhanced ulcer healing by increasing gastric mucosa mucin level and reducing the activity of pepsin (Sabiu et al., 2015). It thus indicates that *S. mombin* extracts could be as effective as other conventional drugs in treating gastric ulcer.

86.3.7 ANTICANCER EFFECT

Spondias mombin leaf extract contains a considerable quantity of vitamins A and C, which are antioxidants. Hence, could protect against cancers (Igwe et al., 2010). Furthermore, the anti-inflammatory potential of *S. mombin* has been reported (Ayoka et al., 2008). Carotenoid isolates of *S. mombin* exerted cytotoxic effect on breast cancer cells by antagonizing apoptosis protein X-linked inhibitor and by enhancing cell death (Metibemu et al., 2020). In a study, extracts of *S. mombin* leaves exhibited cytostatic effects on MDA-MB-231 tumor cells. Furthermore, cell migration and angiogenesis were also inhibited (Rey-Blanes et al., 2020).

86.3.8 ANTIMICROBIAL EFFECT

Spondias mombin is reported to have antibacterial, anti-fungal, and anti-viral effects (Akube et al., 1983). It also has anti-psychotic, soporific, anti-diarrheal, anti-epileptic, anti-inflammatory, cyto-toxicity proficiencies (Adediwura and Kio, 2009). A tea of *S. mombin* leaves is also known to confer soothing effects for gastrointestinal pathogens, uropathogens, and throat inflammations.

Pertaining to its natural activities, antibacterial, and antifungal action of the bark, root including the leaf extracts of *Spondias mombin* on a wide-ranging variety of beta-lactamase-producing enterobacteria has been established. It has also been stated that, the plant extracts (aqueous, methanol, and ethanol) of the leaves of *S. mombin* have antiviral properties on herpes simplex viruses (HSV-1) (Corthout et al., 1991); marked antibacterial properties against *B. cereus*, *Mycobacterium fortuitum* and *Streptococcus pyogenes* have also been reported by (Corthout et al., 1994). Aqueous and ethanolic extracts (EEs) of leaves of *Spondias mombin* were found to inhibit the growth of some gram-positive and gram-negative bacteria (Ajao et al., 1985). The EE was found to be more effective than the aqueous extract in inhibiting bacterial growth.

However, in the case of Bossou et al. (2020) showed that the plant is used for treating several contagions like urinary tract as well as salmonellosis infections. Scientific basis was look in, to study chemical and biological valorization of *S. mombin*. The results obtained showed the presence of some metabolites like flavonoid, tannins, reducing sugar, anthraquinones, and coumarins recognized for their mutable biological activities. Meanwhile, result of antibacterial activity shown look interesting was prominent on the resistant strains of *Staphylococcus aureus, Streptococcus* spp., *Citrobacter* spp*.,* and *Klebsiella pneumoniae*. It was noted that this plant is a good antimicrobial property, antioxidant, and antibacterial agent. Abo et al. (1999) reported that leaf and stem bark of the plant has been shown to exhibit antimicrobial potential comparable to gentamicin and ampicillin.

86.3.9 HEPATOPROTECTIVE EFFECT

Nwidu and colleagues have reported the ability of *Spondias mombin* extract to exert hepatoprotection against carbon tetrachloride (CCl_4)-induced liver injury (Nwidu et al., 2018). Biomarkers of liver injury such as alanine and aspartate amino transferases and alkaline phosphatase (ALP) were elevated in CCl_4-induced liver injury. However, *Spondias mombin* extract lowers the circulating levels of the liver injury enzymes in CCl_4-treated rats. The mechanism involved in *Spondias mombin* hepatoprotective effect include enhanced antioxidant action against oxidative damage in the hepatocytes, hepatocyte cell membrane stability, and repair of damaged hepatic tissues (Nwidu et al., 2018).

86.3.10 ANTI-DIABETIC AND HYPOLIPIDEMIC EFFECTS

Impaired glucoregulation, abnormal lipid metabolism and oxidative injury have contributed to the pathogenesis of diabetes and its associated complication. Nkanu and colleagues reported that *Spondias mombin* extract reduce blood glucose and excess lipid accumulation in diabetic rats implying that it has hypoglycemic and hypolipidemic in diabetic condition (Nkanu et al., 2016). Diabetes is a chronic metabolic disorder associated with impaired glucoregulation, dyslipidemia, and oxidative damage (Soto et al., 2002). Interestingly the hypoglycemic action of *Spondias mombin* in this study was not only noticed in diabetic rats but also in *Spondias mombin* only treated rats suggesting that *Spondias mombin* extract may contain bioactive constituents with capabilities of enhancing blood glucose reduction possible to improved insulin sensitivity or enhanced regeneration of pancreatic β-cell (Nkanu et al., 2016).

In addition, *Spondias mombin* extract ameliorate diabetes induced dyslipidemia by reducing the elevated circulating levels LDL-c, triglyceride, VLDL-c, and total cholesterol (TC) in alloxan-induced diabetic rats (Nkanu et al., 2016). Hence, *Spondias mombin* extract may be protective against diabetes complications such as atherosclerosis, endothelial dysfunction and arterial stiffness which are central risk factors for the pathogenesis of hypertension and other cardiovascular diseases (Wierzbicki and Mikhailidis, 2002).

Alongside, the hypolipidemic and hypoglycemic actions of *Spondias mombin* extract, Nkanu, and coworkers reported that it has antioxidant properties associated with reduced LPO and increased SOD and catalase (CAT) activity in diabetic rats (Nkanu et al., 2016). The anti-diabetic effect of *Spondias mombin* extract was also reported by Ajiboye and coworkers in a study of experimental streptozotocin (STZ)-induced diabetes where they observed reduction in diabetes-associated hyperglycemia, indicated by improved glucose tolerance. The mechanistic pathway involved in *Spondias mombin*-induced hypoglycemia may be through increased adiponectin level but not glucose transporter 4 (GLUT4) (Ajiboye et al., 2018). Adiponectin has been reported to be associated with improved insulin sensitivity and enhanced glucoregulation (Perseglin et al., 2003; Goldstein and Scalia, 2004).

Study on the glucose reducing potency of *Spondias mombin* in rats induced with alloxan by Sugandha et al. (2020) indicated that there was a decline in glucose and total protein (TP) levels but there was no difference in the levels of triglyceride, TC, alanine transaminase, aspartate transaminase and

LPO in extract treated diabetic rats from control. Adediwura and Abo (2009) showed that the antidiabetic effect of a ME of yellow mombin resulted in fasting glucose suppression in a rat model of non-insulin dependent diabetic mellitus with its chloroform fraction reaching a zenith hypoglycemic level at 60.6%. Fred-Jaiyesimi et al. (2009 reported that that maximum reduction in fasting blood glucose of 41.4% was observed an hour post-administration of leaf extract of the plant. They also attributed the hypoglycemic effect of the plant to its inhibitory effect on alpha-amylase and alpha-glucosidase activities. Studies by Ajiboye et al. (2018) indicated that 21 day pre-treated with 750 mg kg^{-1} and 50 mg kg^{-1} of the plant altered glucose uptake in diabetic rats through an increase in adiponectin expression.

86.3.11 ANTIDIARRHEA AND ANTIVOMITING EFFECT OF S. MOMBIN

Several studies have been conducted and observations recorded on the traditional use of *S. mombin* for diarrhea, vomiting, wounds, inflammation, and hemorrhoids treatment. Many studies have also revealed the inflammation suppressive activity of *S. mombin* stem where ellagate was examined and alluded to be the active bio-agent responsible for the therapeutic effects. The extracts obtained from the bark were analyzed through HPLC-DAD-UV as well as TLC.

86.3.12 ANTIMALARIAL EFFECT

Muhammad et al. (2019) conducted an experiment on the potential of *Spondias mombin* as an antimalarial agent that could be utilized through drug formulation and conversion. The bioactive agents in the plant like quercetin and hyperin (quercetin-3-O-β-D-galactopyranoside) were extracted by the authors through different solvent system and extraction techniques. Further structural elucidation and spectral analysis were carried out using infra-red, ultraviolent, and Nuclear magnetic resonance (NMR). The authors studied the antimalarial role through therapeutic and suppression of *Plasmodium berghei* inoculated mice. The authors reported that there was chemosuppressive activity of the tested extract when compared with the standard drug chloroquine. Therefore, the study revealed a new strategy for increasing the herbal use of *S. mombin* peels due to its antimalarial activity and prospects.

86.3.13 ANTIHELMINTHIC ACTIVITY

Ademola et al. (2005) investigated the antihelminthic activity of ethanolic and aqueous extracts of *Spondias mombin*. The mean percentage fecal egg reduction of sheep drenched with 500 mg/kg S. mombin extracts was 15.0%, 27.5%, 65.0%, 65.0%, 100.0% against *Haemonchus* spp., *Trichostrongylus* spp., *Oesophagostomum* spp., *Strongyloides* spp. and *Trichuris* spp. respectively, on day 12.

KEYWORDS

- **acetylcholinesterase**
- **antimicrobial activity**
- **cardioprotective effects**
- **hepatoprotective effect**
- **malondialdehyde**
- ***Spondias mombin***

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CHAPTER 87

Medical Attributes of *Breynia disticha* J.R. Forst. & G. Forst.

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87.1 INTRODUCTION

The majority of numerous people dwelling in the rural area of numerous countries absolutely depend on herbalists and traditional healers that could administer herbal drugs as available remedies for the treatment of human diseases. Therefore, there is a need to intensify effort in search of medicinal plants that could be applied alternative medicine and safe complementary to synthetic drugs that could be utilized for treatment of diverse diseases. A typical example of such plant is *Breynia disticha* J.R. Forst. & G. Forst. belonging to the Phyllanthaceae family. Synonyms of this plant include *Breyenia nivosa* (W.Bull) Small, *Breynia axillaris* Spreng. and *Phyllanthus nivosus* W. Bull. *Breynia disticha* has been described as a shrub with snowy leaf, which is common during the winter season. This plant is well-distributed

in tropical Africa, particularly in Nigeria commonly called ogwueze by local tribe in southern Nigeria (Okokon, 2015; Enwelum et al., 2021).

87.2 BIOACTIVES

Umeokoli et al. (2017) investigated chemical constituents of leaves of *Breynia disticha* (Syn.: *B. nivosa*) where isolation of two novel amide products breynivosamides, dioxopiperazine derivatives breynivosines along with seven famous compounds. The structural components were interpreted HRESIMS as well as NMR (1D and 2D) data along with through assessment using literature. The whole isolated compounds were subjected to test for the antimicrobial as well as cytotoxic activities. Out of several of the isolated compounds, cristatin revealed cytotoxicity against the mouse lymphoma cells in the same vein with IC_{50} value of 13.9 μM despite the fact breynivosamide showed reasonable antimicrobial properties against *Mycobacterium tuberculosis* by means of MIC value of 25 μM.

Okokon et al. (2015) reported that *Breynia disticha* (Syn.: *B. nivosa*) possess antimalarial activities due to the presence of flavonoids, alkaloids, quassinoids, tannins, glycosides, starch, proteins, and saponins. These compounds are secondary metabolites with strong antipyretic effects. Generally, these biomolecules can chelate with nucleic acid base pairing of the parasite or cause protein inhibition as a mechanism of antiplasmodial effects.

Onyegbule et al. (2014a, b) evaluated certain ethnomedicinal application of leaves of the plant such as toothaches, tooth infections, and headaches. The studied plant was extracted using ethanol as a solvent which was fractionated by means of ethyl acetate (EAE), dichloromethane (DCM) as well as methanol. The preliminary phytochemical investigation of the plant was assessed and the anti-inflammatory, antimicrobial along with analgesic activities of the fractions/extracts were carried out. From the result, it was deduced that the plant leave has a high concentration in flavonoids and alkaloids while starch, glycosides, and tannins were present in reasonable quantity.

In ethno-botanical essence, *Breynia disticha* (Syn.: *B. nivosa*) is used in the management of headaches, bacterial-causing dental infections (Onyegbule et al., 2014a, b). The authors also reported several biological activities of the leaf which include its antimicrobial effectively. Amadi et al. (2007) also stated the antibacterial antagonistic action of aqueous and ethanol extracts of the *Breynia disticha* leaf against *S. mutans* enumerated during the

treatment of patients suffering from tooth infection which could be linked to microbial activity.

87.3 PHARMACOLOGY

87.3.1 ANTIMALARIAL ACTIVITY

Okokon et al. (2015) demonstrated the antimalarial potential of the extract in *Plasmodium berghei*-infected mice. The activity of antiplasmodial in the early stage with the contagions and prophylactic properties were examined. Pyrimethamine 1.2 mg/kg along with artesunate 5 mg/kg were utilized as positive controls. They improved their average lifespan to 27 from 11 days. The properties of extract were relatively compared to that of the pyrimethamine (standard drugs). The antipyretic and antiplasmodial effects possibly will in part be facilitated by means of the chemical components of the study plant.

Breynia disticha has been reported to act as antioxidant agents due to the presence of breynivosamides A and B, asperphenamate, breynioside A, cristatin A, robustaside A (E)-p-coumaric acid, lygodinolide, 3-O-$-D-xylopyranoside (166)-$-D-galactopyranoside, Kaempferol, and blumenol A. These biomolecules have been reported and known to be utilized as antiplasmodial (Ammar et al., 2018). Many other biomolecules such as terpenes (triterpenes, sesquiterpenes, diterpenes) and alkaloids derived from this plant are also reported to possess antiplasmodial properties.

87.3.2 CARDIOVASCULAR EFFECTS

Impaired glucose regulation is a known risk factor for cardiovascular disease development. Ezekwesili and Ogbunugafor (2015) reported that *Breynia disticha* possess hypoglycemic effects. In their study, it was reported that many people suffer from diabetes mellitus (DM) resulting into high rate of mortality across the globe due to macrovascular and microvascular complications. Many plants particularly *B. disticha* can be utilized anti-diabetic agent due to its phytochemical composition such as, tannins, cyanogenic glycosides, saponins, cardia glycosides and flavonoids, which can act as antioxidant, analgesic, anti-inflammatory, and antihypertensive agent.

87.3.3 NERVOUS EFFECTS

Neurodegeneration has been reported to be caused by oxidative stress, thus *Breynia disticha* have been shown to be very useful plant with high level of active biomolecules that can mitigate the detrimental effects of free radicals (Ezekwesili and Ogbunugafor, 2015).

87.3.4 ANTIOXIDANT EFFECTS

Breynia disticha is a rich source of flavonoids. Other bioactive compounds including saponin, phenols, cyanogenic glycosides, tannin, sterols, and alkaloids have also been identified in its leaf extract (Ezeigbo et al., 2017). This is the basis of its antioxidant and other health-boosting effects (Oyedemi et al., 2018). *Breynia disticha* extracts showed a strong ABTS radical scavenging potential (Oyedemi et al., 2018).

In a study, *B. disticha* leaf MEs increased spermatogenesis as indicated by increased weights of the epidydimis and testes. Furthermore, ME of *B. disticha* caused the elevated level of testosterone (Ukwubile et al., 2018). The enhanced spermatogenesis and androgenesis observed in male albino rats could be due to the rich presence of flavonoids in *B. disticha* (Ukwubile et al., 2018). This suggests the role of antioxidants in spermatogenesis and androgenesis.

There is evidence that flavonoids play significant roles in hematopoiesis. Significant dose-dependent increase in white and red blood cells were observed in male albino rats to which *B. disticha* extract was administered (Ukwubile et al., 2018).

87.3.5 ANTI-INFLAMMATORY AND ANALGESIC EFFECT

Breynia disticha has both anti-inflammatory and analgesic effects. Efficacy of its anti-inflammatory effect compared favorably with conventional drugs like diclofenac (Onyegbule et al., 2014). Plausible mechanism of its anti-inflammation is via inhibition of histamines and/or serotonin (Onyegbule et al., 2014). The anti-inflammatory effect of *B. disticha* could be via inhibition of COX-2, inflammatory chemokines and cytokines as well as inhibition of transcription factors including PI3K/Akt and kappa kinase/c-Jun amino-terminal kinases (Kopustinskiene et al., 2020).

87.3.6 ANTI-CANCER EFFECTS

Breynia disticha is a promising herb for the treatment of cancers due to its high content of flavonoids. The cytotoxic effect of *B. disticha* could be via mechanisms involving the arrest of the cell cycle, induction of apoptosis, autophagy as well as modulation of the activities of ROS-scavenging enzymes (Kopustinskiene et al., 2020).

There is evidence that flavonoids are bi-functional in ROS homeostasis. They are potent antioxidants in physiological condition. However, they trigger the apoptotic pathways in cancerous conditions (Hadi et al., 2000; Link et al., 2010). As antioxidants, they enhance the stimulation of enzymes with antioxidant capacity while inhibiting the activities of enzymes capacity for oxidation. Furthermore, they demonstrate ROS-scavenging effects (Youn et al., 2006). It was reported that flavonoids inhibited the epidermal growth factor receptor/mitogen activated protein kinase, protein kinase B (Akt), phosphatidylinositide 3-kinases (PI3K) and nuclear factor kappa B (NF-kB) pathways (Kopustinskiene et al., 2020).

87.3.7 HYPOGLYCEMIC EFFECTS

Administrations of aqueous extract resulted in relatively higher glucose suppressing effect in alloxan-induced diabetic rats (Ezekwesili and Ogbunugafor, 2015).

87.3.8 ANTIMICROBIAL ACTIVITY

Onyegbule et al. (2014a, b) reported that methanol, EAE and dichloronethane leaves extracts of *B. disticha* (Syn. *B. nivosa*) moderately inhibited *B. subtilis* and *S. aureus* (gram-positive bacteria) and *S. typhi* (gram-negative bacterium) but innocuous to *A. fumigates* and *C. albicans* (fungal isolates).

87.3.9 HEPATOPROTECTIVE EFFECTS

Ammar et al. (2018) in the quest to understand phytochemical characteristics and the health benefit of aerial components of the plants discovered that Quercetin 3-O-β-D-xylopyranoside and β-D-galactopyranoside, isolates obtained from 70% aqueous ME protected against liver cancer and reduced increased

levels of aspartate transaminase, alanine transaminase, alkaline phosphatase (ALP), total bilirubin and low hepatic NO content through normalization of antioxidant defense. Enwelum et al. (2021) reported contrary effects of *Breynia nivosa* as hepatotoxic effects of the ethanol extract of the leaf. It was revealed that the antioxidant enzymes of the liver were significantly reduced after administration of the extract and also the authors noted that the extract resulted into elevation of many liver enzymes such as AST, ALT, and ALP. Thus, they suggested that the consumption of this plant must be with caution.

KEYWORDS

- **antiplasmodial effects**
- ***Breynia disticha***
- **hypoglycemic effects**
- **nuclear factor kappa B**
- **pharmacology**
- **phosphatidylinositide 3-kinases**

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CHAPTER 88

A Systematic Review of Traditional Uses, Phytoconstituents, and Pharmacological Properties of the Genus *Pimpinella* (Family: Apiaceae)

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88.1 INTRODUCTION

The genus *Pimpinella* is having 152 species across the world (POWO, 2019). Plants perennial, biennial or annual herbs. Upper leaves multisect, pinnately divided. Lower leaves simply pinnate, ternate, often entire or finely divided (occasionally with a wide range of variations among the population). Inflorescences compound umbels with bracts and bracteoles. Calyx teeth obsolete or small. Petals variable in form with white, cream or light pink in color. Carpophore deeply bicleft. Fruit slightly compressed laterally, ovoid to oblong with a broad commissure. Mericarp with 5 filiform ribs; stylopodium depressed conical with the clubbed stigmatic surface. Seed slightly concave on commissural face (POWO, 2019).

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Pimpinella species have been traditionally used by the healers in China, Korea, Lebanon, Palestine, Turkey, Iran, Egypt, the United Kingdom, and Italy since long ago to treat various diseases (Tepe and Tepe, 2015). Seeds of the genus are used as a wild vegetable, in folk medicines, and pharmaceutical industries because of its volatile oil composition. Some species were cultivated by Egyptians, Romans, and Greeks for their aromatic seeds used in various medicine and as a condiment. In German, European, and British Pharmacopoeia, it has been mentioned that fruits are used in cooking and medicinal purposes. Seeds are utilized as diuretic drugs, appetizers, and tranquilizers in Turkish traditional practice (Aydin et al., 2016). They are traditionally used as carminative, expectorant, antidepressant, insecticidal, mutagenic, antispasmodic, nematocidal, estrogenic, antiseptic, antimicrobial, antimalarial, sedative, analgesic, diuretic, anti-depressant, anti-spasmodic, and anti-inflammatory agent (Nasir and Yabalak, 2021).

Seeds and leaves of *P. anisum* are widely used as culinary ingredients (in salads and in pickling) and as a traditional remedy in the local health traditional medicine systems of different civilizations. Essential oil of the seed recommended as an antiseptic, antioxidant, antimicrobial, antispasmodic, expectorant, estrogenic, galactagogue, antidiabetic, insecticidal, anti-inflammatory, carminative, diuretic, appetizers, disinfectant, sedative, analgesic in migraine, and diuretic agents (Rebey et al., 2018, 2020; Ghosh et al., 2019; Hashem et al., 2018; Janahmadi et al., 2008). It promotes menstruation and acts as a mild tonic to treat insomnia, when few seeds are taken in hot milk. The anise tea is traditionally consumed to reduce bronchial asthma, flatulence, and respiratory problems in children. Herb is traditionally recommended throughout the pregnancy period to facilitate the childbirth and in the treatment of constipation in Brazil. It is also used to treat dyspnoea, expectorant, lozenges, and digestive irregularities. The seed oil is also used to eradicate head lice, body lice, and itching insects (Farzaneh et al., 2018; Nasir and Yabalak, 2021). Aqueous infusion of seeds is reported as a wound healer and also shown positive effects against hypoglycemia. Along with the medicinal applications, it is also used in flavoring medicines, chewing gum, toothpaste, ice cream, etc. (Farzaneh et al., 2018). It is widely used in foodstuffs and as a key ingredient in alcoholic beverages (anisetta, sambuca, mistra, anisette, pastis, ouzo, mastic, raki, and arak), non-alcoholic beverages (herbal tea), confectioneries (cakes, candies, etc.), bakery products (bread, cookies, donuts, and maritozzi), and in oral care products (toothpaste and mouth rinse) (Iannarelli et al., 2018). In Persian medieval medicine, the fruit

essential oil is used to treat cerebrovascular diseases and some neurological disorders such as epilepsy and seizures (Karimzadeh et al., 2012).

P. olivieroides and *P. anisoides* are traditionally used as an analgesic, antiseptic, epileptic carminative, diuretic agent. They are used in treating fits, depression, asthma, menstrual disorders as well as in liquor and confectionery industries. *P. saxifraga* and *P. major* are used as tonic, in treating hoarseness, pharyngitis, tracheitis, and liver failure, throat infection, angina, cough vitality and to regain the nerve senses. Fresh roots are chewed to treat toothache, tongue paralysis and inflammatory disorders. They are also used to prepare a tincture for pharynigitis, sore throats, larynigitis, and bronchitis. In traditional therapeutic medicine, *P. brachycarpa* is used in treating persistent cough, bronchial asthma, gastrointestinal problems, and insomnia (Nasir and Yabalak, 2021).

88.2 BIOACTIVES

Pradhan et al. (1994) isolated and structurally elucidated a novel furochromone dimer compound pimolin from the chloroform extract (CE) of *P. monoica* seeds through multidimensional ^{1}H and ^{13}C NMR spectroscopy. Baser et al. (1996) analyzed water distilled essential oil of *P. aromatica* growing in Turkey through GC-MS and found methyl chavicol (91.96%), (E)-anethol (7.22%) and α-pinene (0.12%) as the major compounds.

Velasco-Negueruela et al. (2003) analyzed essential oil of the aerial parts of *P. junoniae*, growing in Spain, Canary Islands, La Gomera, and identified 43 components through GC-MS. Major compounds were α-zingiberene (20.6%), α-pinene (17.9%), (E)-β-farnesene (9.3%), ar-curcumene (7.4%), β-phellandrene (7.0%), β-bisabolene (6.1%) and epoxypseudoisoeugenyl 2-methylbutyrate (6.0%), β-sesquiphellandrene (3.0%), cis-β-guaiene (1.5%), α-phellandrene (1.5%) and α-bisabolol (1.3%). Tabanca et al. (2005) also analyzed essential oil from root, stem, leaves, and fruits of *P. aurea*, *P. corymbosa*, *P. puberula* and *P. peregrina*. In all, 140 compounds were identified with significant qualitative and quantitative differences. In fact, the chief constituents of each species were different and among which only the seed oil shared the principal compound, epoxy pseudoisoeugenyl-2-methyl butyrate (26.8–42.8%). Monoterpenes were dominated in the stem and leaves of *P. aurea* followed by leaves, stem, and fruits of *P. puberula*.

Velasco-Negueruela et al. (2005) analyzed the essential oil composition of aerial parts of two endemic species (*P. anagodendron* and *P. rupicola*) growing in Tenerife, Spain, and the Canary Islands. Compounds *viz*. β-bisabolene (34.8%), limonene (10.9%) and α-zingiberene (10.5%) were the leading constituents of *P. rupicola* flowering tops (flowers + unripe fruits). Whereas α-zingiberene (32.9%), β-bisabolene (17.9%), β-pinene (15.8%) and ar-curcumene (11.5%) reported from the flowering tops of *P. anagodendron*. Tabanca et al. (2006) carried out GC-MS analyzes of essential oils (EOs) extracted from 15 various *Pimpinella* species and identified 140 constituents. Amongst all, the essential oil obtained from roots of all the species shared the same major compound, epoxypseudoisoeugenyl-2-methylbutyrate (20 to 82.6% composition).

Delazar et al. (2006) performed different chromatography techniques to isolate two phenylpropanoid compounds viz. erythro-1′-(4-methoxyphenyl)-propan 1′,2′-diol and erythro-1′-[4-(sec-butyl)-phenyl]-propan-1′,2′-diol from the active dichloromethane (DCM) extract of aerial parts of *P. aurea*. Fakhari and Sonboli (2006) reported 32 compounds and among which, methyl eugenol (34.0%), limonene (26.6%), elemicin (6.9%), sabinene (6.7%) and perillaldehyde (5.2%) were the major constituents of *P. barbata*. Mirza et al. (2007) analyzed the hydro-distillated volatile oil from the aerial parts of *P. deverroides,* and 29 components were identified. Major constituents detected in the oil were iso-geijerene (20.3%), dictamnol<trans-> (14.5%), pregeijerene (11.3%) and anethole <E-> (9.1%). Safaei-Ghomi et al. (2009) analyzed the dried aerial parts of *P. aurea* from central Iran and identified 26 compounds; in which, main components were β-caryophyllene (13.6%), β-bisabolene (12.2%), (E)-β-farnesene (10.4%) and β-sesquiphellandrene (10.2%). Maggio et al. (2013) characterized the EOs from different parts of *P. tragium* subsp. *glauca*. Among all, C-12 nor-sesquiterpene was the major class of metabolites (56.6–70.6%) and compounds geijerene (28.9–49.3%) and pregeijerene (10–19.1%) were identified as predominant compounds.

Figueredo et al. (2015) performed GC-MS analysis of essential oil extracted from the aerial parts of *P. isaurica* cultivated in South Anatolia and identified 53 compounds. The major constituents were sabinene (12.79%), myrcene (4.43%), geijerene (24.30%), terpinene-4-ol (4.71%), dictamnol (5.82%), caryophyllene oxide (3.84%). Ghosh et al. (2019) carried out a study on the nutritional quality parameters and safety assessment of seeds of two *P. anisum* cultivars in Bangladesh Spice Research Center. Trans-anethole (83.67%), fenchone (5.29%) and 1,2-diisopropenylcyclobutane (6.31%) were observed in higher quantities. In addition, Rebey et al. (2019)

investigated the chemical composition of *P. anisum* fatty acids and EOs of seeds from Egyptian, Serbian, Tunisian, and Turkish populations at three different developmental stages. In all accessions, maximum oil yield was achieved at the stage of full maturity, ranged between 11.93 (Serbia) and 13.80% (Tunisia). Fatty acid profiling of seed oil was characterized by high proportions of palmitic (4.90–57.18%) and petroselinic (10.48–46.60%) acids. Trans-anethole (66.34–93.05%) was detected during ripening in all accessions. The main phenolic compound was naringin (17.55–32.49%) and its accumulation was followed by syringic, gallic, ellargic, and rosmarinic acids during ripening stage. Rebey et al. (2020) investigated the effect of different drying methods on essential oil and phenolic contents of *P. anisum* seeds. A significant increase in the percentage composition of trans-anethole (84.21%), and estragole (3.82%) were found in the samples processed through shade drying method. However, higher composition in the total phenol and flavonoid contents were also recorded in the shade dried sample (42.70 mg of GAE/g and 53.55 mg of QE/g, respectively). In all drying procedures studied, naringin (41.04–43.76%), chlorogenic acid (23.13–27.19%) and rosmarinic acid (12.26–15.95%) were the predominant phenolics.

Recently, Karik and Demirbolat (2020) have isolated the essential oil from *P. enguezekensis*ec fruits, and the major components detected were trans-anethole (86.8%), methyl chavicol (4.8%), followed by pseudoisoeugenol 2-methylbutyrate (3.5%) (Figure 88.1).

88.3 PHARMACOLOGY

88.3.1 CENTRAL NERVOUS SYSTEM (CNS) STIMULATING ACTIVITY

The influence of essential oil obtained from dried ripened fruits of *P. anisum* on the functions of the central nervous system (CNS) was studied through hot plate, impairment of motor coordination, forced swimming and elevated plus maze tests in mice model (Samojlik et al., 2012). Analgesic activity of essential oil showed highly significant prolongation of latency responses at 30th min of treatment. However, the motor impairment caused by the drug midazolam (5 mg/kg) in the animals pretreated with the essential oil showed significant results in the inability of treated animal to stay on the rotating rod until 20th minute of the drug treatment. It was found that the application

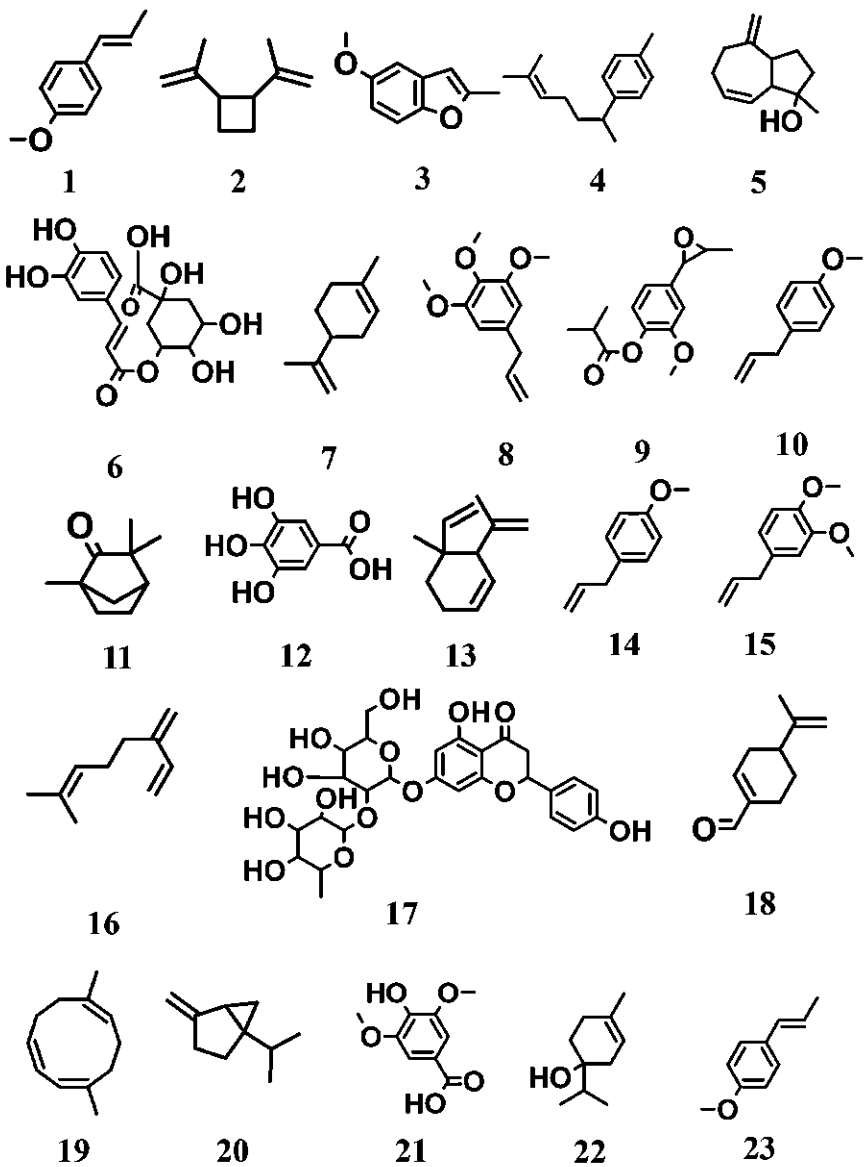


FIGURE 88.1 Structures of (E)-anethol (1); 1,2-diisopropenylcyclobutane (2); 5-methoxy-2-methylbenzofuran (3); α-curcumene (4); dictamnol (5); chlorogenic acid (6); D-limonene (7); elemicin (8); epoxy pseudoisoeugenyl-2-methyl butyrate (9); estragole (10); fenchone (11); gallic acid (12); geijerene (13); methyl chavicol (14); methyl eugenol (15); myrcene (16); naringin (17); perillaldehyde (18); pregeijerene (19); sabinene (20); syringic acid (21); terpinene-4-ol (22); and trans-anethole (23).

of codeine in the essential oil treated animals showed latency responses continuously (Samojlik et al., 2012).

88.3.2 AMELIORATIVE EFFECT

Abdul-Hamid and Gallaly (2014) investigated the ameliorative effect of *P. anisum* oil (5 ml/kg) on an artificial sweetener aspartame (ASP) induced to Wistar rats. Marked changes in the purkinje and granular cells with deeply stained cytoplasm was observed, followed by myleinated nerve fibers with thickenings and splitting in the ASP-treated animals. However, ultrastructural examination of purkinje cells showed dilated rough endoplasmic reticulum, condensed mitochondria, with few nuclei in the granulation cells, which displayed the efficacy of essential oil against neurotoxicity.

88.3.3 ANTISPASMODIC AND MUSCLE RELAXANT EFFECTS

Tirapelli et al. (2007) carried out antispasmodic and muscle relaxant activities of *P. anisum* hydroalcoholic extracts [40% ($HA_{40\%}$), 60% ($HA_{60\%}$) or 80% ($HA_{80\%}$)] of aerial parts in anococcygeus smooth muscle of rat. Extracts (50 µg/mL) inhibited acetylcholine-induced contraction significantly. However, the $HA_{60\%}$ relaxed the acetylcholine-pre-contracted tissues (31.55 ± 3.56%) in a dose dependent passion (5–50 µg/mL). In contrast, $HA_{40\%}$ and $HA_{80\%}$ did not show any muscle relaxant activities. Further, authors also found that incubation of the tissues with N^G-nitro-L-arginine methyl ester (L-NAME) significantly upregulated the contraction induced by acetylcholine, which indicated its inhibitory role of nitric oxide (NO) in modulating the muscle contracting responses in the smooth muscle. These findings provided functional evidence for the antispasmodic and muscle relaxant potentiality of *P. anisum* extract.

88.3.4 ANTI-INFLAMMATORY EFFECT

Iannarelli et al. (2018) evaluated the anti-inflammatory activity of *P. anisum* essential oil on lung inflammation caused by lipopolysaccharide (LPS). The tracheal epithelial cells (HBEpC and HTEpC) were treated with LPS and incubated with essential oil (0.3%). The levels of pro-inflammatory cytokines such as IL-8 and IL-1β were carried out using RT-PCR and Western Blot

analysis. The compound: (E)-anethole was found as predominant compound (97.9%) and it could significantly decrease IL-1 and IL-8 expression levels followed by increase in the Muc5ac protein secretion levels in LPS-treated HBEpC and HTEpC cells.

88.3.5 MILK PRODUCTION IN RATS

The efficacy of aqueous and EEs (0.5 and 1 g/kg) of *P. anisum* seeds on milk production in rats was analyzed (Hosseinzadeh et al., 2014). Assessment of milk production was done by measuring the weight of the pups during the suckling period and LD_{50} of both the extracts were 4.93 and 3.77 g/kg, respectively. Extracts significantly increased the milk production in treated groups (68.1 and 81%) than the control animals (Hosseinzadeh et al., 2014).

88.3.6 INSECTICIDAL ACTIVITY

Insecticidal activity of nanoemulsion containing 81.2% (E)-anethole from the essential oil of *P. anisum* was evaluated against *Tribolium castaneum* adults and F1 progeny (Hashem et al., 2018). The nanoemulsion showed significant impact on its progeny (LC_{50} of 9.3% v/v).

88.3.7 CARDIOVASCULAR ACTIONS

Pontes et al. (2019) carried out cardioprotective activity of *P. anisum* aqueous extract of seeds in normotensive and Kyoto Wistar rats. Administration of aqueous extract (0.25–2 g/kg/day, p.o.) showed a dose-dependent reduction in blood pressure values. Administration of 100 mg/kg aqueous extract reduced mean arterial pressure by 43% in relation to the control group (110 ± 7.3 mmHg) due to changes in the diastolic blood pressure, followed by increase in the intervals between heart beats (by 129%) at par the control (0.14 ± 0.02s). Both the responses were immediately reversed, suggesting the occurrence of physiological mechanisms that control blood pressure, such as the baroreflex.

88.3.8 ANTI-ULCEROGENIC EFFECTS

Al-Mofleh et al. (2007) carried out antiulcerogenic activity of *P. anisum* seed aqueous suspension (250 and 500 mg/kg). Pretreatment of rats with aqueous

suspension 250 mg/kg significantly prevented gastric mucosal lesions and the ulcer indices were found to be 6.00 ± 0.51, 4.66 ± 0.80, and 6.00 ± 0.44, respectively. Similarly, stomach treated with 500 mg/kg aqueous suspension showed the ulcer indices 4.00 ± 0.44, 3.66 ± 0.66, and 4.00 ± 0.51 in ethanol, sodium hydroxide and sodium chloride groups, respectively.

88.3.9 ANTICANCER ACTIVITY

Different concentrations of a sesquiterpene compound pimpinelol isolated from *P. haussknechtii* was treated against MCF-7 and MDA-MB cells (Aghaei et al., 2018). Pimpinelol showed a dose dependent cytotoxic effect (IC_{50} 45 and 25 μM, respectively). Higher dosage of pimpinelol (80 and 100 μM) reduced viability of MCF-7 and MDA-MB cells as compared to 1 μM doxorubicin (positive control). Quantitative fluorescence intensity showed an increase in aggregated proteins in MCF-7 cells as compared to positive and negative controls. Results indicated that pimpinelol induced protein aggregation and endoplasmic reticulum stress in MCF-7 human breast cancer cell lines.

88.3.10 ANTIMICROBIAL ACTIVITY

EOs and MEs obtained from the aerial parts of *P. anisum* seeds were evaluated for their single and combined antibacterial activities against the different strains (Al-Bayati, 2008). EOs and ME recorded the promising antibacterial activities against most of the pathogens using broth microdilution method. Higher antimicrobial efficacy of EO and MEs (MIC 62.5 g/mL) were observed against *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris* and *Bacillus cereus*. Combination of EOs and ME showed an additive effect against *P. aeruginosa*.

Efficacy of major ingredients and essential oil isolated from *Pimpinella enguezekensis*, *Pimpinella anisetum, P. tragium* subsp. *glauca* and *Pimpinella flabellifolia* have been reported against several pathogens (Tepe et al., 2006; Maggio et al., 2013; Karik and Demirbolat, 2020).

88.3.11 ANTIOXIDANT ACTIVITY

The antioxidant activity of *P. enguezekensis* essential oil was evaluated through DPPH radical scavenging and β-carotene/linoleic acid (β-carotene bleaching, BCB) assays. Results revealed that the antioxidant activity of the essential oil was significantly higher due to the presence of bioactive

components. Antioxidant activities of *P. enguezekensis* fruit oil revealed the appreciable DPPH radical scavenging activity. The extract exhibited higher radical scavenging (IC_{50} 10.15 µg/mL), reducing power (EC_{50} 187.24 µg/mL) and metal chelating capabilities (IC_{50} 6.85 mg/mL) than essential oil (IC_{50} 114.87 µg/mL, EC_{50} 548.05 µg/mL and IC_{50} 58.65 mg/mL, respectively) (Rebey et al., 2020).

It was found that *P. anisetum* essential oil exerted greater DPPH free radical-scavenging activity than that of *P. flabellifolia* oil with IC_{50} value 5.62 ± 1.34 µg/mL. Similarly, in β-carotene/linoleic acid test system, the essential oil of *P. anisetum* found promising than *P. flabellifolia* with 70.5% ± 2.86% inhibition (Tepe et al., 2006). Moreover, Farzane et al. (2018) also reported a significant antioxidant activity of *P. anisum* seeds against DPPH and FRAP free radicals.

88.3.12 ANTICONVULSANT EFFECTS

Pourgholami et al. (1999); and Karimzadeh et al. (2012) performed anticonvulsant activity of *P. anisum* fruit essential oil in mice. The oil did not induce statistically significant disturbance in motor coordination up to a dose of 1 mL/kg at 30 min post-administration period. However, at the dose (1 mL/kg or higher) of the essential oil caused severe sedative effects after 20 minutes of the treatment. Essential oil (0.5, 0.75, and 1 mL/kg) significantly suppressed PTZ-induced HLTE and mortality [ED_{50} 0.52 (0.35–0.76) mL/kg] and further blocked significantly HLTE and mortality with an i.p. [ED_{50} 0.20 (0.12–0.33) mL/kg].

KEYWORDS

- **anticonvulsant effects**
- **artificial sweetener aspartame**
- **central nervous system**
- **essential oils**
- **NG-nitro-L-arginine methyl ester**
- ***Pimpinella***

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