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Bioactives and Pharmacology of Medicinal Plants

VOLUME 1



T. Pullaiah
Editor



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T. Pullaiah, PhD



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AAP Focus on Medicinal Plants

ABOUT THE SERIES

This new book series, edited by T. Pullaiah, focuses on bioactives and pharmacology of medicinal plants.

For millennia, medicinal plants have been a valuable source of therapeutic agents, and still many of today's drugs are based on plant-derived natural products or their derivatives. Bioactive compounds typically occur in small amounts, and they have more subtle effects than nutrients. Bioactive compounds influence cellular activities that modify the risk of disease and help to 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, antibacterial, antifungal, antioxidant, anticancer, anti-inflammatory, antidiabetic, hepatoprotective, cardioprotective, nephroprotective properties as well as other protective effects on the liver, kidney, heart, and nervous system.

The volumes aim to be comprehensive desk references on bioactives and pharmacology of all the medicinal plants. They will also be important sourcebooks for the development of new drugs.

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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, Faculty of Biosciences, Head of the Department of Botany, Head of the Department of Biotechnology, and Member of Academic Senate. He was the 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. Under his guidance, 54 students obtained their doctoral degrees. He has authored 52 books, edited 23 books, and published over 330 research papers, including reviews and book chapters. 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 was also a member of the Species Survival Commission of the International Union for Conservation of Nature (IUCN). Professor Pullaiah received his PhD from Andhra University, India, attended Moscow State University, Russia, and worked as Post-Doctoral Fellow during 1976–1978.



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Abbreviations

4-OHT	4-hydroxytamoxifen
AChE	acetylcholinesterase
AFB1	aflatoxin B1
AgNPs	silver nanoparticles
AGS	against gastric cell lines
AIA	adjuvant-induced arthritis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AM	<i>Aegle marmelos</i>
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BP	blood pressure
BuChE	butyrylcholinesterase
CaOx	calcium oxalate
CAT	catalase
CD	Crohn's disease
CFA	complete Freund's adjuvant
cGMP	cyclic guanosine monophosphate
CHD	coronary heart disease
CHX	chlorhexidine gluconate
CNS	central nervous system
COSY	correlated spectroscopy
COX	cyclooxygenase
CTM	Chinese traditional medicine
CVD	cardiovascular disease
DA-EO	<i>D. ambrosioides</i> essential oil
DBP	diastolic blood pressure
DEN	diethyl nitrosamine
DM	diabetes mellitus
DMPD	dimethyl p-phenylenediamine dihydrochloride
DNBS	dinitrobenzene sulfonic acid
DPHH	2,2 di (4-tert-octylphenol)-1 picrylhydrazyl
DPPH	1,1-diphenyl-2-picrylhydrazyl
DSS	dextran sulfate sodium

DW	dry weight
EA	early antigen
EAC	Ehrlich ascites carcinoma
EBV	Epstein-Barr virus
ER	estrogen receptor
Es	estrogen
ESBL	extended-spectrum β -lactamase
ETEC	enterotoxigenic <i>E. coli</i>
EtOAc	ethyl acetate
FBS	fast blood sugar
Fe NTA	ferric nitrilotriacetic acid
FRAP	ferric reducing antioxidant power
FSH	follicle-stimulating hormone
FST	forced swim test
GC-MS	gas chromatography-mass spectrometry
GD	growth delay
GDH	glutamate dehydrogenase
GFR	glomerular filtration rate
GOT	glutamate oxaloacetate transaminases
GPT	glutamate pyruvate transaminases
GPX	glutathione-peroxidase
GSH	glutathione
GST	glutathione S-transferases
GSTT	gross saponine extract of <i>T. terrestris</i>
HAE	hydroalcoholic extract
HCl	hydrochloride
HCV	hepatitis C virus
HDL	high-density lipoprotein
HEK	human embryo kidney
HFD	high-fat diet
HIV	human immune virus
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear single quantum correlation
HOCS	herbal oral contraceptive suspension
HPTLC	high-performance thin-layer chromatography
HSV	herpes simplex virus
HTS	high throughput screening
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome

IDH	isocitrate dehydrogenase
IL	interleukin
ISO	isoproterenol
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LH	luteinizing hormone
LLC	Lewis lung carcinoma
MABA	micro-plate Alamar blue assay
MBC	minimum bactericidal concentration
MBL	metallo-beta-lactamase
MCV	mean corpuscular volume
MDA	malondialdehyde
MDA	methane dicarboxylic aldehyde
MDH	malate dehydrogenase
MEP	methyl erythritol-4-pathway
MIC	minimum inhibitory concentration
miR	micro-RNA
MMP-2	metalloproteinase-2
MRSA	methicillin-resistant <i>S. aureus</i>
NBP	L-3-N-butylphthalide
NF- κ B	nuclear factor- κ B
NMR	nuclear magnetic resonance
NPD	normal pellet diet
PBMC	peripheral blood mononuclear cells
PCM	paracetamol
PCOS	polycystic ovarian syndrome
PGE2	prostaglandin E2
PIs	protease inhibitors
PKB	protein kinase B
PM	plasma membrane
PPE	polyphenolic extract
PPS	psyllium polysaccharide
PRF	phenolic rich fraction
PTZ	pentylene-tetrazole
RBL	rat basophilic leukemia
RGC's	retinal ganglion cells
RT-PCR	reverse transcriptase-polymerase chain reaction
SBP	systolic blood pressure
SCFA	short-chain fatty acid

SDH	succinate dehydrogenase
Se-NPs	selenium nanoparticles
SOD	superoxide dismutase
STZ	streptozotocin
SULT	sulfotransferase
TBARS	thiobarbituric acid reactive substances
TFL	tail-flick latency
THP	Tamm-Horsfall protein
TKS	traditional knowledge system
TNF	tumor necrosis factor
TNFR	TNF receptor
TPA	12-O-tetradecanoylphorbol-13-acetate
TRN	triclosan
TST	tail suspension test
UA	uric acid
UGT	UDP-glucuronosyltransferase
UTI	urinary tract infection
VDT	volume doubling time
VRE	vancomycin-resistant enterococcus
XOD	xanthine oxidase activity
ZI	zone of inhibition
γ -GT	γ -glutamyl transpeptidase

Preface

Plants, since time immemorial, have been a valuable source of medicine. They are the source of many bioactives, and many of the present medicines are based on plant-derived natural products or their derivatives. The phytochemicals influence metabolic activities that modify the risk of disease and alleviate disease symptoms. A variety of bioactives and therapeutics from medicinal plants have been reported, which include antiviral, antimicrobial, antioxidant, anti-cancer, anti-inflammatory, and antidiabetic, hepatoprotective, nephroprotective, and cardioprotective activities.

In this two-volume book, the bioactives and pharmacology of some important medicinal plants are given. A brief introduction is given for each species. Under each species, bioactive compounds are listed, and their chemical structures are given. It is followed by their pharmacological activities. All the published literature on pharmacological activities on that species is reviewed. I hope that this will be a sourcebook for the development of new drugs.

I request the readers give their suggestions for improvement of future editions.

I am thankful to all the authors who contributed to the review chapters. I thank them for their cooperation and erudition.



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CHAPTER 1

Bioactives from Botanicals: An Overview

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1.1 INTRODUCTION

All wealth comes from the bosom of the Earth, said Adam Smith (1776), considered by many as the father of modern economics. This wealth is in the form of resources of the Earth, which may be either be used directly or after due modifications and/or processing. These resources are often classified into two major categories: biotic and abiotic (Bergstrom and Randall, 2016). These two resource categories form integral components of the four major domains of the Earth: atmosphere, lithosphere, hydrosphere, and biosphere. The four domains are intrinsically and closely connected with each other through various types of biogeochemical cycles. Abiotic resources include air, water, soil, and rocks and all their chemical constituents, as well as all types of physical radiation. Biotic resources include plants, animals, and microbes (which together form the biosphere), and all other organic materials produced by and derived from them (Mather and Chapman, 2014). Of these three types of living organisms, animals, and many microbes show heterotrophic modes of nutrition and have to depend on inputs from the autotrophic organisms such as plants and a few microbes such as chemosynthetic and photosynthetic bacteria. Plants, by virtue of their capacity to harvest light energy and to utilize simple inorganic chemicals such as water and carbon dioxide, are able to synthesize a variety of organic molecules and thus constitute the major producers of the Earth. They also form the basic organisms, which initiate the complicated food and energy chains and webs that are very vital to the sustenance of the biosphere as well as of the other domains of the Earth, making the whole Earth as a single, self-regulating, complex super-organism (Lovelock, 2016).

1.2 BOTANICALS

Merriam-Webster Dictionary (2016) defines a botanical, in an adjective form, as: (i) of or relating to plants or botany; (ii) derived from plants; or (iii) a species of plants, and, in a noun form, as a substance obtained or derived from a plant or its parts. This dictionary also provides at least 21 synonyms, antonyms, idiomatic expressions, and related words for botanicals such as herbal, herbaceous, biological, agricultural, floral, vegetable, arboreal, horticultural, phylogenetic, etc. Americans often use this word in much the same way as they use prescription pharmaceuticals or over-the-counter medicines supplied by pharmacies to treat disease symptoms, prevent ailments or to maintain health and well-being. In this sense, botanicals are nearly synonymous with bioactives. Based on their bioactivity, botanicals are broadly classified into pharmaceuticals, nutraceuticals, and cosmeceuticals. In these categories, whole plants or their parts may be used directly, or their pastes, extracts or isolated purified chemicals are used.

1.3 CHEMISTRY OF BOTANICALS

Chemicals from plants are called phytochemicals or metabolites that often form the end products of plant metabolic processes; some of these are also intermediates formed in metabolic pathways. Thus, metabolites may be products of primary (or central), intermediate or secondary (specialized) metabolism (Pott et al., 2019). The boundary between these three are, often, is not very clear; neither it is easy to classify certain chemicals as belonging to any one of these three categories. For example, polyamines have the look of primary but are really secondary and sirenins and turgorins have the look of secondary but are really primary in nature. There is also disagreement among researchers in classifying certain phytochemicals into any one of these three categories (for example, certain amino acids and fatty acids).

1.3.1 *Primary Metabolites*

Primary metabolites are those which are directly involved in the growth, development, and reproduction of plants and invariably perform intrinsic physiological functions that are absolutely vital for the survival of the plant. These metabolites are the results of primary metabolic processes of plants such as photosynthesis, respiration (glycolysis, TCA cycle and fermentation),

pentose phosphate pathway, etc., and form source chemicals from which secondary metabolites are formed. Primary metabolites are universally present in plants. Primary metabolites are often concentrated and/or stored in fruits, seeds, vegetative storage organs such as tubers, bulbs, corms, and rhizomes, roots, leaves, and sometimes even in stems of plants. These are used as and when they are needed for various physiological processes. In general, plant primary metabolites needed for commercial use are high-volume but low value bulk chemicals and are primarily used as foods, food additives, and industrial raw materials. These are mainly fatty acids and vegetable oil/fats, various types of carbohydrates (mono-, di-, tri-, tetra-, penta-, hexa-, and polysaccharides of homo- and hetero-categories), amino acids, peptides, and proteins and purine and pyrimidine bases of nucleic acids.

1.3.2 Secondary Metabolites

Secondary metabolites, unlike primary metabolites, are of limited distribution among plants and are often restricted to specific taxonomic groups (Wink, 2008, 2016). Many secondary metabolites are found in very small quantities and often in traces and are not bulk chemicals like primary metabolites. Secondary metabolic pathways originate from “different nodes of core primary metabolic pathways” and are mostly derived from a few major building blocks like shikimic acid, amino acids and acetyl Co-A through the following secondary metabolic pathways: shikimic acid pathway (starting with shikimic acid), malate/acetate (polyketide) pathway, mevalonic acid (mevalonate pathway-starts from acetyl CoA), amino acid pathway and methyl erythritol-4-pathway (MEP pathway, starting with glyceraldehydes-3-phosphate) (Figure 1.1).

The fact that many secondary metabolites are found in taxonomically unrelated families (for example, camptothecin in Icacinaceae, Nyssaceae, Rubiaceae, Apocynaceae, Loganiaceae, etc., and cardiac glycosides in Scrophulariaceae, Apocynaceae, Asclepiadaceae, Ranunculaceae, Brassicaceae, Hyacinthaceae, Liliaceae, Celastraceae, and among animals in toads and some beetles) raises two viewpoints: (i) secondary metabolites are the results of parallel evolution of the different taxonomic groups or (ii) they are the result of specific endophytes which occur in unrelated plant groups. That the secondary metabolites are the products of endophytes and not of plants in which they occur or they are products of interaction between plants and endophytes is gaining more support in recent years (Ludwis-Müller, 2015; Ogbe et al., 2020).

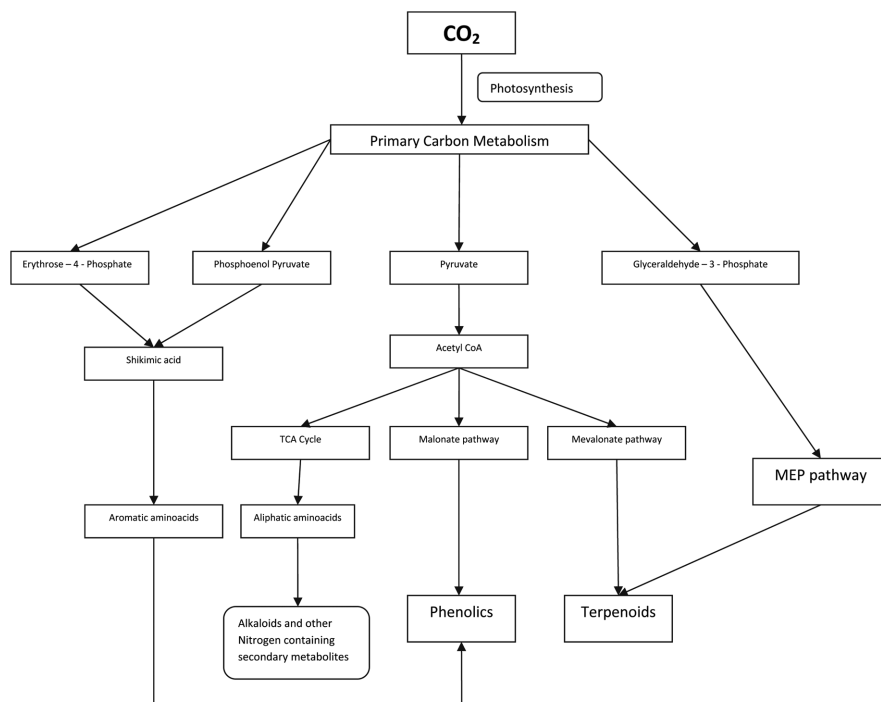


FIGURE 1.1 Secondary metabolic pathways.

Secondary metabolites are conveniently classified into two major categories: (i) those with nitrogen and (ii) those without nitrogen (Wink, 2008, 2016). Examples for the former include amines, alkaloids, non-protein amino acids, cyanogenic glucosides, glucosinolates, alkamides, lectins, many peptides, etc. Examples of the latter include terpenes like monoterpenes (including iridoid glucosides) sesquiterpenes, diterpenes, triterpenes, sterols, and saponins (including cardiac glycosides) and tetraterpenes, phenolics like phenylpropanoids, coumarins, lignans, flavonoids, anthocyanins, tannins, and polyketides (anthraquinones) and others like polyacetylenes and organic acids.

Out of over 1 million known natural products 200,000–250,000 are believed to have some sort of bioactivity. In the entire plant kingdom, the known secondary metabolites amount to around 600,000–700,000 of which about 150,000–200,000 are bioactive. In the higher plants, of the known 500,000–600,000 secondary metabolites approximately around 100,000 are bioactive (Thirumurugan et al., 2018). Out of these the structure of at least around 54,900 (exactly 54,910) has been described (Wink, 2016)

(i.e., around 30,000 are nitrogen containing and the rest around 24,900 are without nitrogen).

Secondary metabolites are believed to be not primarily involved in growth, development, and reproduction of plants (Salisbury and Ross, 2005; Evans, 2009), but their role in these processes cannot be totally set aside (Haslam, 1994). Many views have been put forward so far on the role of secondary metabolites (Demain and Fang, 2000) and they are as follows: (i) The earliest expressed view is that they are waste or ergastic substances (Hartmann, 2007); (ii) some believe that these have obscure value or no explicit value; (iii) Hans Krebs who deciphered TCA cycle believed that they are ballistic compounds that have neither beneficial nor harmful effects; (iv) some secondary metabolites are involved in growth regulation (e.g., gibberellins), intra-, inter-, and extra-cellular communications (e.g., jasmonates) or as signaling compounds that help to attract pollinators, fruit/seed/spore dispersers, and symbionts (Wink, 2008, 2016; Evans, 2009); (v) Secondary metabolites provide flavors, taste, aroma, and color to the plants and their parts; and above all (vi) they play very important ecological roles such as combating/tolerating /resisting various types of biotic and abiotic stresses. They, thus, help in increasing the fitness and survival value of plants.

Whatever role the secondary metabolites play in plants that possess them, there is no doubt that they, as bioactives, have been very useful to humans in various ways, particularly as medicines for various human ailments. Some primary and intermediary metabolites are also of medicinal importance. Many metabolites serve both nutritive and healthcare functions and, thus, serve as nutraceuticals.

1.4 IDENTIFICATION AND CHARACTERIZATION OF BOTANICALS AND THEIR BIOACTIVES WITH PARTICULAR REFERENCE TO MEDICINAL PROPERTIES

1.4.1 Bioprospecting

Ever since their appearance on this Earth, humans have been using plants for many of their requirements. This is particularly true for plants needed for health care. Initially, they chose useful medicinal plants found around them by aping other mammals, particularly apes, dogs, pigs, and cattle that chewed the needed medicinal plants. Later on, they experimented on randomly chosen plants on a trial-and-error basis for their various ailments. Thus, there slowly emerged man's traditional knowledge system (TKS) about

medicinal plants and nutraceuticals in various indigenous societies of the world. Such a TKS has indicated that there is now clearly a range of higher plants from which to choose the desired medicinal plants. But yet, there is still a lot remains to be done in fully exploiting the existing plant resources. For example, the Royal Botanic Gardens (2016), at Kew conservatively estimated in 2016 only 17810 medicinal plants. Allkin in 2017 reported 28,817 medicinal plants and Salmerón-Manzano et al. estimated in 2020 that only 10% of all vascular plants (totally 350,000–500,000 vascular plants are estimated to occur on this Earth) are medicinal. These numbers account only for a very small percentage of the World's plants that contribute on a global scale to health care. Hence, there is an urgent need for exploring World's plant wealth for the identification of potential medicinal plants.

The act of looking for useful plants is called by the term bioprospecting (=biological prospecting; biodiversity prospecting). Bioprospecting may be defined as follows: The systematic and organized searching for plants (as well as animals and microbes) from which useful and valuable materials can be obtained (Paterson and Lima, 2017; Kariali and Behera, 2019) which find use in plant-based industries either through unique bio-processing or through novel end or by-products (Eisner, 1992; Reid et al., 1993). Later on, the scope of this term was enlarged by incorporating the exploration of plants (and other living organisms) for useful biomolecules (=chemoprospecting) and for the useful genes that are responsible for the production of novel biomolecules (=gene prospecting).

The increased interest in bioprospecting is attributed to the following facts (Krishnamurthy, 2003): (i) A slowdown in innovations in the chemical and pharmaceutical industries; (ii) the rise of biotechnology as a dominant impacting factor in the operation of these industries; (iii) the deep concern over the observed rapid and irreversible biodiversity loss and an urgency to exploit the biodiversity elements before they are lost; (iv) the invigorated attempt by many developing communities to search for new avenues to exploit and use their bioresources; (v) rapid advances in the techniques of bioprospecting and above all (vi) the need for critical and exhaustive bioprospection of medicinal resources has increased in view of the facts that newer diseases are emerging and that many disease-causing microbes have developed resistance to some of the already available drugs/molecules/medical formulations.

There are three approaches to/methods of bioprospection (Krishnamurthy, 2003): (i) Random approach: It involves the random selection of plants in any given area for an analysis of their potential value and use. This is a very time-consuming approach and may or may not yield the desired results. (ii)

Phylogenetic approach: It involves the collection and analysis of members of those families in which some taxa are already known to be good sources of useful chemicals. This is a comparatively less time-consuming approach than the previous one, and the possibility of obtaining successful results is greater. (iii) Ethno-directed approach: This approach is much superior to the first two. Here, attention is specifically focused on plants, which, based on TKS of indigenous communities, are known to be useful but yet are not popularized or analyzed for their chemical constituents. In other words, this approach is exploiting a ready-made knowledge that is sure to yield the desired results. Additionally, it is the least time-consuming and least expensive among the three approaches.

1.4.2 Characterization of Botanicals and Their Bioactives

There are four steps involved in bioprospection: (i) collection of selected plants following any one of the three approaches mentioned above; (ii) isolation, identification, and characterization of the chemical substances of these selected plants; (iii) screening for bioactivity of the isolated chemicals and confirming their activity; (iv) product development and testing followed by commercialization. Recent biotechnological tools and sophisticated methods and instrumentation enable the isolation and critical analysis of the diversity of chemical substances of the selected plants based on their structure determination. The development of very sensitive and highly specific bioassays to detect even picograms of potentially useful biomolecules and automated screening technology allow screening thousands of plant samples at a very quick pace and efficiently select those with value in bioindustries (Komen, 1991; Mayr and Bojanic, 2009).

1.4.2.1 Conventional Pharmacognosy and Pharmacognosy

Pharmacognosy may be defined as the study of the biological, biochemical, and physical properties of potential or actual drug substances of natural origin; it also includes the search for new drugs from natural sources. In broader terms, it also includes a critical study of the source materials for drugs, such as plants (and its parts), animals (and their products), and minerals and salts. Thus, essentially pharmacognosy includes (i) the identification of the sources of natural drugs; (ii) authentication through determination of the morphological, structural, and chemical features of these natural sources

(using macroscopic, microscopic, and phytochemical methods), and DNA-based analyzes; (iii) distinction of genuine drug sources from substitutes and adulterants (Elufioye and Badal, 2017).

Pharmacology may be defined as the study of drugs and their application and therapeutic use in medicine (Katzung et al., 2012). It also includes the study of the actual mechanism of action of these drugs, their targets, and toxicology (including side effects) in the living cells/tissues. It covers two aspects (Olson, 2019): Pharmacodynamics that deals with the chemical interactions of drugs with the body (i.e., molecular, biochemical, and physiological effects of drugs) and pharmacokinetics that deals with absorption, distribution, metabolism, and excretion of the drugs. Thus, pharmacology deals with the living body's reaction to administered drugs.

Conventional pharmacognosy and pharmacology studies have provided us detailed information about the sources of natural drugs, their identification, authentication, characterization, and mechanism of action in the living body. Conventional pharmacology involves a laboratory to clinical approach and, if we follow it, from target identification to developing a medicinal product, it takes 10 to 15 years and from 1 to 15 billion US Dollars of expenditure. Conventional pharmacognosy uses a natural resource such as a plant to discover a new bioactive compound. In other words, it is a process that starts in a natural resource and ends up in the production of a new useful bioactive molecule. Till now, both these fields of scientific activity have helped us to select and analyze several thousands of medicinal plants for their bioactives and have brought to light several of them as detailed earlier in this chapter. Pharmacological and clinical studies have been parallelly carried out on many of these bioactives. However, the performances of both these are not to the desired pace since the World Health Organization has estimated that nearly 80% of World population depends on traditional medicine, mostly plant-based (Farnsworth et al., 1985; Smith-Hall et al., 2012). TKS sources reveal that the wealth of medicinal plant resources of the World is so enormous that the pace of performance of conventional pharmacognosy and pharmacology is not enough. For example, the total number of medicinal plants known to all the ethnic communities in India is around 3700 and veterinary medicinal plants is around 1,500 (Pullaiah et al., 2016–2017), that hardly 15–20% of these alone have so far been subjected to critical pharmacognostic and pharmacological analyzes.

1.4.2.2 *Reverse Pharmacognosy and Reverse Pharmacology*

In view of the above, the concepts of reverse pharmacognosy and reverse pharmacology have been proposed within the last 20 years. Both of them aim at an accelerated drug discovery (Saeidnia et al., 2016). The term reverse pharmacology was first introduced in 2001 by Takenaka. It may be defined as “the science of integrating documented clinical experimental hits into leads by exploratory studies and further developing these into drug candidates by experimental and clinical research.” In other words, reverse pharmacology involves a clinic to laboratory approach, unlike conventional pharmacology which involves a laboratory to clinic approach. It is also called target-based drug discovery. It accelerates the clinical candidate development (Patwardhan and Vaidya, 2010) and, thus, serves as a fast-track path for drug discovery (Arulsamy et al., 2006). Reverse pharmacology involves three phases: (i) experimental phase which includes robust documentation of clinical observations of a drug molecule; (ii) exploratory phase in which studies relating to tolerability of the drug molecule, drug interactions, range of dosages to be given, etc., are made with patient to whom the drug is administered; and (iii) basic and clinical experimental phase to identify and validate the reverse pharmacological correlates of drug molecules. In classical pharmacology, we start from a plant (or other organisms) and finally get the useful drug molecule but in reverse pharmacology we start with knowing which drug molecule would affect a key enzyme, target or physiological function and then trying to find out which other plants could be a source of a drug molecule that would affect the same key enzyme, a target or physiological function.

The term reverse pharmacognosy was first introduced in 2006 by Do and Bernard (2006). While classical pharmacognosy, as discussed earlier, studies natural products as sources of new drug leads and effective drug development, reverse pharmacognosy, a complementary to the conventional discipline, couples combinational chemistry, high throughput screening (HTS), virtual screening and databases, especially TKS databases in the process of accelerated, fast track drug discovery. It aims towards finding new biological targets for a natural compound/drug molecule by virtual or real screening and, in that process, identifies new natural resources (plants, animals, and microbes) that contain these active molecules. Instead of proceeding from plants to drug molecules as in classical pharmacognosy, reverse pharmacognosy proceeds from drug molecules to new plant sources of these molecules (Do et al., 2014). Since it involves TKS databases on medicinal and other

useful plants, sure, and successful results will be obtained within a shorter time and at a cheaper cost.

1.5 FUTURE PERSPECTIVES ON BIOACTIVES AND BOTANICALS

It has been very clearly established till now that bioactives from botanicals have very great potential in human welfare. There is an ever-growing demand for many of these bioactives in medicine and other fields. However, the achievements made in this regard have been very limited. Large-scale, fast, critical, and successful screening of these metabolites is needed in the near future so that useful products such as medicines can be manufactured on an industrial scale. The following aspects need to be given the greatest attention in future to achieve the above goal:

1. Fast and efficient screening of Earth's biodiversity through intense bioprospecting and conventional and reverse pharmacognosy and pharmacology. In this process, enough emphasis should be given to integrate the very rich TKS available with the indigenous communities throughout the World.
2. Large-scale chemical synthesis of useful biomolecules already known should be undertaken as they are available only in traces or in very small quantities in natural biotic resources.
3. In addition to chemical synthesis, greater attention should be focused in future on metabolic engineering coupled with or without synthetic biology. Metabolic engineering tried to optimize cellular processes, which are often 'endemic' to specific organisms, in the production of a chemical compound of interest from a substrate that is preferably cheap and simple (Garcia-Grados et al., 2019). Although only a very limited success has so far been achieved in metabolic engineering, it will, in the future, "rival and potentially eclipse synthetic organic chemistry" (Kealing, 2010). Such molecules produced by metabolic engineering will no doubt, be "designer molecules."
4. The potential of biotransformation processes should also be exploited in the future. Biotransformations have obtained greater importance in practice as a complementary or support for chemical synthesis or in the conversion of one natural product into another desired natural product. Biotransformation may help to "enlarge or sequentially degrade or specifically modify" synthetic or natural chemicals,

and for this microbial, plant, or mammalian cells and their cell-free enzymes can be used as tools.

5. The importance of endophytes in secondary metabolite production by plants that harbor them has already been referred to. Increased attempts are now being made to produce secondary metabolites by the endophytes isolated from the associated plants. However, large-scale production of desired secondary metabolites from such isolated endophytes has not been achieved in many cases (Tidke et al., 2019). Therefore, in future, attempts towards this goal should be given greater attention.
6. In future, there should be more studies to understand the mode of action of bioactives in the target organisms (humans or domestic animals) identifying target/receptor sites to specific drugs, understanding drug-docking site structure using computational and mechanistic studies, drug structure-activity relationships, toxicology, side-effects, etc.

KEYWORDS

- **biosphere**
- **biotic and abiotic**
- **chemosynthetic**
- **high throughput screening**
- **methyl erythritol-4-pathway**
- **microbes**
- **traditional knowledge system**

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CHAPTER 2

Bioactives and Pharmacology of *Aegle marmelos* (L.) Correa

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2.1 INTRODUCTION

Aegle marmelos (L.) Correa, (AM) a popular tree (Rutaceae) with immense medicinal values available in various parts of India and is known as “Bilva, Maredu, Wood apple Beal, Golden apple, Bengal quince,” etc., in different languages. It is grown in temple gardens, and the leaves were used in worshipping Lord Shiva and the fruits were edible in addition to the traditional medicines, which possessed with high content of phytochemicals besides varied biological activities. The secondary metabolites and volatile oil components of different parts of the bael tree studied extensively and reported notable pharmacological effects against several non-communicable diseases like diabetes, atherosclerosis, cancer, and cardiovascular diseases (CVDs) (Karunanayake et al., 1984).

2.1.1 Distribution

This is native to India and distributed widely and found throughout Indian plains or hill areas and found in “Myanmar, Indonesia, Vietnam, Tibet,

Nepal, Thailand, Sri Lanka, Bangladesh, Cambodia, Laos,” etc. (Sharma and Dubey, 2013).

2.1.2 Botanic Description

It is a medium-sized tropical deciduous tree species, bark gray-white with longitudinal wrinkles, spines with reddish-brown, axillary, leaves trifoliate, aromatic, elliptic, glabrous, flowers white with fragrant in axillary panicles, fruits round berry, woody, oblong or pyriform (Pullaiah and Chennaiah, 1996).

2.1.3 Importance

The wood apples, in addition to the other parts, were potentially used for the healing of “gastric ulcers, dysentery, and chronic diarrhea” in addition to the “laxative and pulmonary” diseases. It is highly appreciated for its medicinal claims in traditional systems and varied pharmacological activities viz., anti-microbial, organ protection, gastric problems, and oxidative stress-related diseases and including cancer (Manandhar et al., 2018).

2.2 BIOACTIVES PHYTOCHEMICALS

The investigative studies for the secondary metabolites from various regions of the globe extensively and reported different classes of chemical constituents such as flavonoids, coumarins, terpenoids, essential oils, fatty acids, terpenoids, alkaloids, amino acids, and phenolic compounds, tannins, etc., have been isolated from its parts (Sharma et al., 1980; Raju et al., 1999; Janarthanan et al., 2012; Chavda et al., 2012; Kumar et al., 2013; Varughese and Tripathi, 2013; Ramya et al., 2013; Victoria et al., 2014; Samanta et al., 2018; Poonam et al., 2019). The systematic analysis on the phytochemicals reported from *A. marmelos* are discussed as follows. Chatterjee and Roy (1957, 1959) elucidated the chemical constituents namely, β -sitosterol (terpene), marmin, marmesin, xanthotoxin, auraptene, umbelliferone, lupeol, 6,7-dimethoxy coumarin, scopoletin, tempamide, skimmianine, skimmin, decursinol, halopine, aegelinol, anthraquinone, marminal, and 7- α methylmarmin from the Heartwood (Yogita and Gulshan, 2011). Thereafter a plethora of secondary metabolites were identified and discussed as in subsections.

2.2.1 Alkaloids

Several nitrogenous secondary metabolites (alkaloids) reported from the leaves *A. marmelos* such as, *O*-3,3-(dimethylallyl)halfordinol, *N*-2-methoxy-2-(4-methoxyphenyl) thylcinnamamide, *N*-2-ethoxy-2-(4-methoxyphenyl) ethylcinnamamide, *N*-2-methoxy-2-[4-(3,3'-1methylallyloxy) phenyl] ethyl cinnamide and marmeline (Manandhar et al., 1978) and *N*-2-hydroxy-2-(4-hydroxyphenyl) ethylcinnamide, Aegeline (Govindachari and Premila, 1983) and Anhydromarmeline by Phuwapraisirisan et al. (2008) and Laphookhieo et al. (2011).

2.2.2 Phenyl Propanidids

The phenyl propanidids were reported from *A. marmelos* include Aegelinoside A and B (Phuwapraisirisan et al., 2008), Marmesin (Shoeb et al., 1973; Chatterjee and Mitra, 1949; Chatterjee and Majumdar, 1971; Phuwapraisirisan et al., 2008), aeglemarmelosine (2-phenyl-5-(4-methoxyphenyl)-D2-oxazoline) (Laphookhieo et al., 2011), Aegelbine-A (7,8-dihydroxy-4-hydrofuroquinoline) and Aegelbine-B (4-hydro-7-hydroxy-8-prenyloxyfuroquinoline) by Mohammed et al. (2016). The phytochemical constituents, namely auraptene, imperatorin, marmisin, glycoprotein, scopoletin, skimmianine, and xanthotoxin were reported and reviewed from various parts of *A. marmelos* (Bhar et al., 2019). Phytochemical screening of the extracts of the leaves reported for the presence of flavonoids, tannins, terpenoids, steroids, cardiac glycosides and saponins (Venkatesan et al., 2009; Sivaraj et al., 2011). In addition, phenolic compounds, inulin, lignin, proteins, carbohydrates, and fatty oils were identified by Ratan et al. (1982), whereas alkaloids, cardiac glycosides, and flavonoids by Rajan et al. (2011). The presence of carotene, allo-imperatorin, psoralen, auraptine, marmin, umbelliferone, lupeol, dimethoxy coumarin, scopoletin, lembamide, marmesin, skimmlamine, luvangetin, imperatorin, xanthotoxin in addition to terpenes and fatty oil which are reported as pharmacologically active phytoconstituents (Bhar et al., 2019).

2.2.3 Terpene Related Constituents

The methanol extract of leaf analyzed by the GC-MS revealed the presence of 33 phytoconstituents reported for various biological effects especially antibacterial activity and the major compounds are, 1-Dodecanol, 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-(1.11), 2,3-dihydro-

3,5-dihydroxy-6-methyl-(1.11), 2,3 Dioxabicyclo [2.2.2] oct-5-ene, 1-Methyl-4-(1-Methyl-ethyl)-(Limonene dioxide 1), bicyclo[3.1.1]heptane-2,3-diol, 2,6,6-trimethyl (2,3-Pinane-1,2-diol), 2-Cyclohexen-1-one, 4-hydroxy-3-methyl-6-(1-methyl-ethyl), Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-(BHT), Tetradecanoic acid (Myristic acid), 2(4H)-5,6,7,7A-Tetrahydro-6-hydroxy-4,4,7a-trimethyl,1,3-cyclohexadiene,2-methyl-5-(1-methylethyl)-(1-Phellandrene), 2-Propenoic acid, 3-(4-hydroxy-3-methoxyphenyl)-, methyl ester (Cinnamic acid, 4-hydroxy-3-methoxy-, methyl ester) and aditerpene, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol (phytol) with significant antibacterial agent. The 9,12,15-Octadecatrienoic acid methyl ester (Linolenic acid methyl ester) claimed for antibacterial and anticandidal activity. The 2-Hexadecen-1-ol, 3,7,11,15-Tetramethyl (Phytol isomer), Octadecanoic acid (Stearic acid), Benzene, 1,2-dimethoxy-4-[(4-methylphenyl) sulfonyl]methyl, fatty alcohols such as Ergost-5-en-3-ol, 3- β -campesterol, Stigmasta-5, 22-dien-3-ol, Stigmast-5-en-3-ol, (3- β) were also reported (Farina et al., 2014).

Ali and Pervez (2004) isolated marmenol, 7-geranyloxy coumarin [7-(2,6-dihydroxy-7-methoxy-7-methyl-3-octaenyloxy) coumarin] from the methanolic extract of the leaves along with trans-cinnamic acid, praealtin D, betulinic acid, 4-methoxy benzoic acid, valencic acid, Np-cis-and trans-coumaroyltyramine, montanine, and rutaretin. The existence of lupeol, aegelin, marmesinin, flavon, rutin, β -sitosterol, eugenol, glycoside, montanine, O-isopentenyl halfordiol, marmelin, and phenyl-ethyl cinnamamides were reported by Guhabakshi et al. (1999), Suriyamoorthy et al. (2014) and Bhar et al. (2019).

The chemical characterization of volatile oil has shown the existence of d-limonene, α -d-phellandrene, cineol, citronellal, citral, p-cymene, and cumin aldehyde. A beneficial product with high limonene content which is used in the hair oils or calico printings formulated from the rind of the wood apple since d-limonene found as the main constituent (Samanta et al., 2018; Mishra et al., 2011, 2016; Kaur et al., 2006; Charoensiddhi and Anurag, 2008), whereas the seed oil is composed of linoleic and linolenic acids, palmitic, stearic, oleic acids (Dhankhar et al., 2011).

2.2.4 Screening Studies of Phytochemical Constituents

The total flavonoid content was estimated using a standard curve of quercetin in methanol and aqueous extract by Sharma et al. (2011a). In addition, salicylate, and three constituents were extracted and characterized from unripe

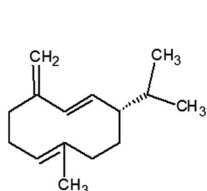
fruit using thin layer chromatography by Sharma et al. (2011b). Many quantification studies of flavonoids in *A. marmelos* were reported (Shailesh and Hemalatha, 2013; Sathya et al., 2013; Kumar et al., 2013, 2016; Garima et al., 2013; Tupe et al., 2013; Ariharan and Nagendra, 2014; Venkatesh et al., 2014). The variation in the distribution of phytochemicals in different solvents were reported and revealed that the toluene extract showed anthocyanins, phenolics, and sterols whereas the chloroform extract reacted positively for the alkaloids, phenols, xanthoproteins, carboxylic acids, coumarins, anthocyanins. The methanol extract reacted positively for xanthoproteins, phenolics anthocyanins, alkaloids, carboxylic acids, flavonoids, and coumarins. Similarly, the aqueous extract showed phenolics, anthocyanins, carboxylic acids, alkaloids, flavonoids, and coumarins (Chavda et al., 2012). The reducing sugars reported in the water and methanol extract (except petroleum ether) of the leaves (Reddy and Urooj, 2013). The phytochemical analysis confirming alkaloids, saponins, flavonoids, and phenolic compounds and yields from the leaf extracts reported by Kumar and Hemalatha (2013) and the estimation phenolic substances reported by Tupe et al. (2013). Marmemine and Fagarine were identified as two pharmacologically active compounds such as 1,2-benzenedicarboxylic and Di-n-octyl phthalate using standardized techniques (Victoria and Samrot, 2015). Main phytoconstituents found in leaves are marmesinine, citronella, aegeline, eugenol, citral, skimmianine, cumin aldehyde, cineol, and lupeol, reported from all parts using HPLC from *A. marmelos* (Figure 2.1) (Nitu et al., 2015).

2.3 PHARMACOLOGICAL ACTIVITIES

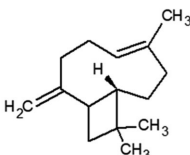
A. marmelos (AM) is a potential medicinal plant which is being used in traditional medicines and proved for various pharmacological effects from different parts of the world. The active principles isolated from various parts of bael tree scientifically proved as therapeutically potent candidates against several diseases like oxidative stress-related diseases viz., diabetes, CVDs, or inflammation-related claims in addition to effective over the infectious diseases or ulcers were proved in certain clinical trials (Maity et al., 2009). The wood apple has been highly appreciated by the scientific world for its biological effects and safety in terms of non-toxic at tested doses. The present review focused on the discussion of pharmacological activities in *in-vitro* or *in-vivo* systems even in the human of clinical trials (Hema and Lalithakumari, 1999; Anonymous, 1989, 1999; Kala et al., 2006; Narayan and Yadav, 2009; Lambole et al., 2010; Sharmila and

Devi, 2011; Dhankhar et al., 2011; Nugroho et al., 2011a; Atul et al., 2012; Pushpendra et al., 2012; Patel et al., 2012; Patkar et al., 2012; Nidhi et al., 2013; Shahedur and Rashida, 2014; Rahman and Parvin, 2014; Shaili et al., 2015; Yogita et al., 2017; Bhar et al., 2019).

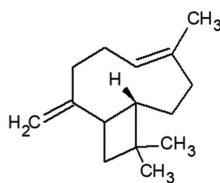
Phytochemicals from *A. marmelos*



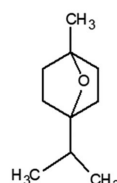
Germacrane-D



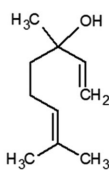
Germacrane-B



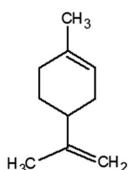
(E)-Caryophyllene



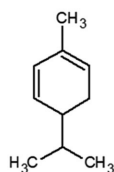
1-8- Cineole



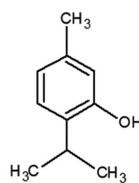
Linalool Oxide



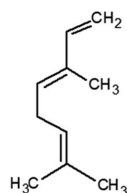
Limonene



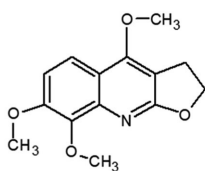
α-Phyllandrene



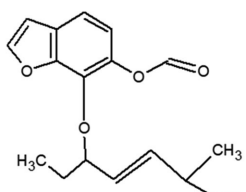
Thymol



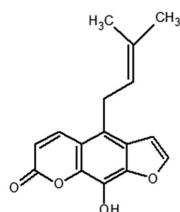
(E)-β-Ocimime



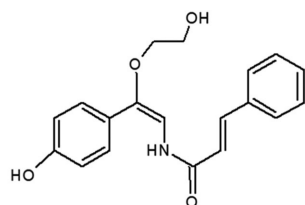
Skimmianine



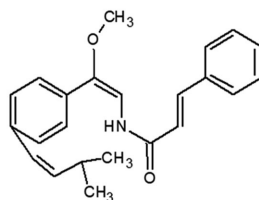
Imperatorin



Alloimperatorin



N-2-methoxy-2-[4-(3',3'-imethylallyloxy)phenyl]ethylcinnamamide



N-2-methoxy-2-(4-methoxyphenyl)ethylcinnamamide

FIGURE 2.1 (Continued)

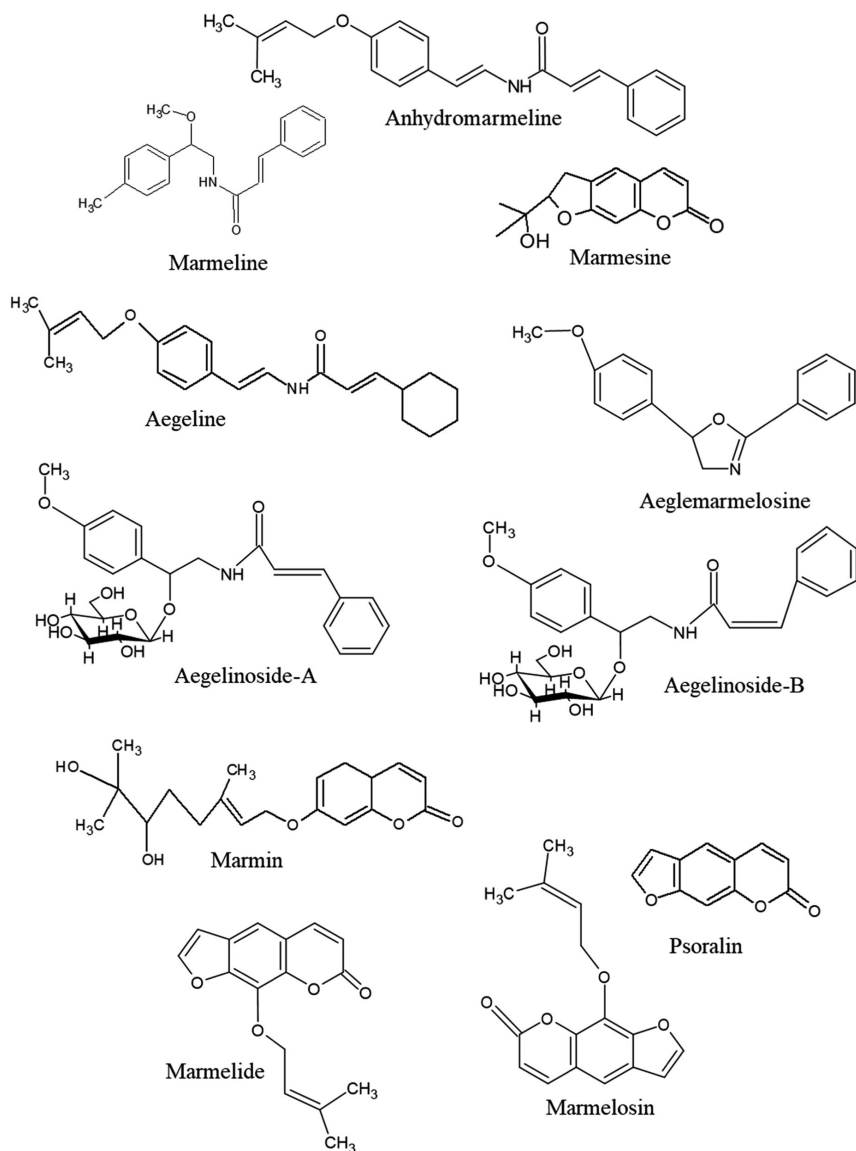


FIGURE 2.1 Phytochemicals from *A. marmelos*

2.3.1 Antiviral Activity

The *in vitro* antiviral activity of extracts and guided fractions from *A. marmelos* were evaluated against human coxsackieviruses (B1 to B6) and reported Marmelide from the stem bark as an active ingredient and found effective in controlling the early stages of infection at the cellular level. The marmelide also effective on the virus of white spot in shrimps (Balasubramanian et al., 2007).

2.3.2 Antibacterial Activity

The antibacterial efficiency of AM was extensively reported by several researchers. Several extracts exhibited noteworthy antibacterial activity against several bacterial strains such as *Salmonella typhi*, *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus vulgaris*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *P. mirabilis*, *Micrococcus luteus*, *Enterococcus faecalis*, *S. faecalis*, *M. glutamicus*, *S. pyogenes*, *B. stearothermophilus*, *M. luteus*, and *Pseudomonas denitrificans* (Rojas et al., 2003; Mohan et al., 2005; Gavimath et al., 2008; Sahara et al., 2008; Suresh et al., 2009; Jyothi and Rao, 2010; Gheisari et al., 2011; Sivaraj et al., 2011; Balakumar et al., 2011; Poonkothai and Saravanan, 2008; Ulahannan et al., 2008; Kothari et al., 2011; Supriya et al., 2012; Victoria et al., 2014, 2015). The extracts were proved active against certain gram-positive bacteria or gram-negative bacteria by the scientists (Mujeeb et al., 2014; Nabaweya et al., 2015; Chinchansure et al., 2015).

2.3.3 Antifungal Activity

The volatile oil of leaves and its constituents were highly effective against the plant pathogenic fungi as well as human pathogenic fungi which were extensively studied (Rana et al., 1997) and the constituents such as 2-isopropenyl-4-methyl-oxa-cyclopenta(β), anthracene-5, 10-dione and β -sitosterolglucoside, stigmasterol, vanillin, and salicin, from the seeds also being effective on *C. albicans* (Mishra et al., 2010) and leaf extracts on fungal species of the skin disease like *Trichophyton rubrum*, *Microsporum canis*, *T. mentagrophytes*, *M. gypseum*, and *Epidermophyton floccosum* with effective minimum inhibitory and fungicidal concentrations (Balakumar et al., 2011; Nabaweya et al., 2015).

2.3.4 Antimalarial Activity

The seed and leaf extracts were reported for its potential antimalarial activity against *Plasmodium berghei* in the *in vitro* or *in vivo* systems. The leaf

extracts did not exhibited effect in the *in vivo* as its affected by the seed extracts (Dhankhar et al., 2011). The leaf extract of *A. marmelos* exhibited a significant effect among the tested plant species against *Plasmodium* species and it exerted very feeble cytotoxicity against the tested HeLa cell lines (Kamaraj et al., 2012).

2.3.5 Antidiarrheal Activity

The raw fruit pulp extract showed a protective effect on the indomethacin or alcohol-induced gastric mucosal damage. The results suggest that it significantly protected at the tested concentrations (Dhuley, 2003). The extracts inhibited the growth of pathogenic *Shigella boydii*, *S. flexneri*, *S. sonnei*, and *S. dysenteriae* (Joshi et al., 2009) Brijesh et al. (2009) demonstrated its effect on Giardia.

2.3.6 Wound Healing Activity

The methanol extract of seeds was potential in wound healing when subjected as injection of an ointment on the incision model or male Wistar rats, and the AME responded significantly as reported by Jaswanth et al. (2001).

2.3.7 Antioxidant Activity

Upadhyaya et al. (2004) demonstrated significant antioxidant effect in diabetic mice by the leaf extract, whereas Bramhachari and Reddy (2010) the radical scavenging effect. The antioxidant activity in relation to phenolics and flavonoids was reported by Siddique et al. (2010) and many scientific reports on the antioxidant potential of various parts of bael tree using various antioxidant methods were reported (Atul et al., 2012; Dinesh et al., 2011; Farina et al., 2011; Sharmila et al., 2011). The reports on the *in vitro* antioxidant activity by Rajan et al., 2011; Gheisari et al., 2011; Sathya et al., 2013; Reddy and Urooj, 2013; Maria and Lavanya, 2019) elucidated *A. marmelos* as a potential natural source for antioxidants. Mujeeb et al. (2017) demonstrated the antioxidant and cytotoxic effects from the 18 varietal samples and concluded Pant Aparna as a more effective medicament through radical scavenging potential with special reference to DPPH or Superoxide radical. In addition, Bera (2017), demonstrated this effect using the gum or arabinogalactan.

2.3.8 Antidiabetic Activity

The leaves as well as fruit pulp of *A. marmelos* has been well studied for its antidiabetic activities and demonstrated in *in vitro* as well as *in vivo* systems. The mechanism has well established and being discussed as follows.

Das et al. (1996) studied the role of leaf extracts on the streptozotocin (STZ) induced diabetic rats and found that they have altered and normalized profile along with dilation of veins, arrangement of hepatocytes, liver fibrosis, glycogen, glomerulus of kidney tubules in addition to regeneration of β -cells, improved functional status of pancreatic integrity at cellular level. Further, the bael leaf extract showed notable antidiabetic efficiency through the restoration of insulin, normalized sugar profile, the usage of *A. marmelos* as potential hypoglycemic agent was supported (Seema et al., 1996).

The leaf extracts were subjected to antidiabetic effect in alloxan-induced rats or rabbits and observed the restoration and normalization in the diabetic profile and the bodyweight (Ponnachan et al., 1993; Kamalakkannan and Prince, 2003; Saha et al., 2016). In addition, the oxidative stress management has been improved by the leaf extracts in alloxan-induced diabetic conditions in rats (Sabu and Kuttan, 2004).

Oral administration of AM extract significantly reduced oxidative stress induced by alloxan. This was evident from a notable reduction in membrane lipid peroxidation and hydroperoxide levels in serum and liver induced by alloxan. Further, the extract enhanced the activities of antioxidant enzyme levels in blood and liver from 9th and 12th day onwards after extract administration (Sabu and Kuttan, 2004). Kamalakannan and Prince (2005) reported the antidiabetic activity of leaf and callus extracts of *A. marmelos* in rabbit was studied by Arumugam et al. (2008).

Narender et al. (2008) demonstrated the blood-glucose-lowering effect by Aegeline-2 in streptozotocin-induced rats and improvement in the diabetic profile. It also significantly improved lipid profile in the hamster model and suggested as a β_3 -AR agonist using simulation studies. The scientific evidence on the extracts of *A. marmelos* in different experimental models and proved that the leaves (Rao et al., 2003), stem bark, fruit, and seeds were effective in management of hypoglycemic activity (Kar et al., 2003; Kesari et al., 2006; Gohil et al., 2010). Even the leaf extracts were demonstrated its antidiabetic effect at mRNA expression of muscarinic M1 receptor and found upregulation in the insulin secretion which supports for the clinical significance in diabetic therapy (Gireesh et al., 2008). The clinical trials by (Mohammad and Mohammad, 2009) by the leaf extract found highly beneficial in the management of postprandial blood glucose in non-insulin-dependent

diabetes management. The immunohistochemical studies of Abraham et al. (2010a), indicated that the extracts were improved the expression of antioxidant down-regulation genes and noticed the enhancement of standard antioxidant marker enzymes/proteins in STZ induced diabetic rats, and also proved the improvement in the neurological responses (hippocampus serotonergic function which found great application in clinical therapies during the diabetes condition (Abraham et al., 2010b). The alcoholic extract of leaves found significant hypoglycemic activity and alteration in the diabetic lipid profile and improvement in high density lipids in addition to significant rise in antioxidant enzymes. The treatment with extract effected on the inflammatory cell counts (Bhatti et al., 2011; Asaduzzaman et al., 2011).

In addition, the bark extracts also being affected the insulin, glycated hemoglobin, total protein, hepatic glycogen, marker enzymes of liver, in STZ induced rats. The histological studies also proven the improvement in the functional integrity of beta cells and sensitivity of insulin (Gandhi et al., 2012). The leaf extracts were significantly controlled the fasting blood glucose and lipid profile and urea of blood, creatine, and renal peroxides and reduced glutathione (GSH), catalase (CAT) in alloxan-induced diabetic nephropathic conditions. The histological studies also supported the findings such as decrease in the glomerular expansion, tubular dilation, and inflammatory cells and exhibited reversal effects and found ameliorative effect improvement of kidney function in the alloxan-induced diabetic rats (Bhatti et al., 2013b).

The ameliorative effect of AM leaf extract on alloxan-induced diabetic nephropathy was evaluated in animal models. The extract strongly reduced FBS, TC, creatinine, blood urea, and TBARS levels in renal tissue. It further enhanced the concentration levels of reduced GSH, CAT than the control animals at 200 mg/kg. Histopathological sections of the renal tissues indicated that the extract exhibited a notable decrease in glomerular expansion, inflammatory cells, and tubular dilation, which indited its protective effect against alloxan-induced diabetic nephropathy (Bhatti et al., 2013b). Gautam et al. (2015) elucidated the mechanism of activity by Aegeline for glucose utilization by the expression of GLUT-4 translocation of sugars in the presence of agonists and proposed an alternate mechanism via stimulation of PI3-kinase-Rac1-PAK1-cofilin pathway in the skeletal muscle cells [C2C12 myotubes].

The significant role of Eugenol obtained from the leaves of *A. marmelos* extract was reported to prevent the advanced glycation end products formation by modulating β -cell function and preventing complications of diabetes in the rat model (Hafizur et al., 2017). Mudi et al. (2017) reported that the leaf and fruit extracts were significantly controlled the blood glucose and

inferred that the tested extracts decreased the insulin resistance in the experimental rats.

2.3.9 Antihyperlipidemic Activity

The leaf hydroalcoholic extract has a significant effect in the reducing the lipid content of triton or high fat diet hyperlipidemic experimental rats at two sublethal doses found inhibition of serum cholesterol and triglycerides in contrast it also improved high density lipid in the serum as compared with standards (Kamalakkannan and Prince, 2005; Krushna et al., 2008; Vijaya et al., 2009; Narayanasamy and Leelavinothan, 2011; Asghar et al., 2018).

2.3.10 Anticancer Activity

Anticancer potential of ethanolic extract and different solvent fractions obtained from AM stem bark was determined against tumor cell lines in *in vitro* methods. The tested extract and fractions exhibited noteworthy antiproliferative activity against different cancer cell lines such as T-lymphoid Jurkat, melanoma Colo38, MDAMB-231 cell lines, leukemic K562, B-lymphoid Raji, erythroleukemic HEL and breast cancer MCF7 (Lampronti et al., 2003). Marmelin, eugenol, cineol, luteol, and d-limonene characterized from *A. marmelos* has been reported as potential anticancer agents (Baliga et al., 2012; Gangadevi et al., 2008; Jagetia et al., 2003; Moongkarndi et al., 2004). Molecular mechanism of marmelin isolated from *A. marmelos* in cancer prevention was investigated by using HCT-116 colon cancer tumor xenografts *in vivo model*. The constituent activated cancer reducing markers such as $TNF-\alpha$, caspase, TNF receptor (TNFR)- and TNFR associated death domain (Dharmalingam et al., 2008). Immunostaining studies indicated that the component strongly reduced macrovesicle formation in treated animals and it also inhibited inflammatory markers such as CoX-2, IL-8, and vascular endothelial growth factor mRNA.

Luciferase reporter and EMSA assays results indicated that marmelin significantly attenuated $TNF-\alpha$ -mediated activation and translocation of nuclear factor- κB (NF- κB). Translocation of NF- κB was further confirmed by Western blot analysis (Dharmalingam et al., 2008). Antiproliferative potential of different Soxhlet extracts such as ethanol, petroleum ether, hexane, and chloroform prepared from shade-dried *A. marmelos* leaves was evaluated using different cancerous cell lines such as IGR-OV-1, MCF-7, A-549, THP-1, PC3 and CoLo-05. Bioassay-guided fractionation of ethanol extract resulted in fractions 2, 4 and 5 exhibited noteworthy inhibition in

THP-1 cells. Further, HPTLC analysis of fraction 2 resulted in identification of furanocoumarin, which may be responsible for the anticancer potential of ethanol extract (Bhatti et al., 2013a).

Scientific studies showed that plant extract can inhibit the increase of leukemic K562, T-lymphoid Jurkat, B-lymphoid Raji, erythroleukemia, Colo38, and MCF 7 and MDA-MB-231. It can even prevent cell proliferation (Sankhe and Jangda, 2017). The ethanolic extract of *A. marmelos* leaves showed significant cytotoxicity effect against MCF-7 breast cancer cells in 24 hours. The ethanolic extract (20–200 µg/ml) inhibited the cell proliferation by more than 85% at its maximum concentration with an IC₅₀ of 54.19 µg/mL. The results suggested that the tested extracts inhibited the growth of MCF-7 breast cancer cells in a very effective way (Maria and Lavanya, 2019). The essential oil of Beal leaf showed anticancer activity in human tumor cell lines such as PSN-1, LoVo, H157 and ovarian (2008) cells, respectively (Poonam et al., 2019).

2.3.11 Ulcer Healing Potential

Anti-ulcer potential of *A. marmelos* seeds methanolic and aqueous extracts was investigated against indomethacin-induced ulceration, pylorus ligation induced ulcerations and stressed induced ulceration. In a study, the ulcer was artificially induced by using indomethacin, stress, and pylorus. Methanolic extract showed potential anti-ulceration impact. It showed its mechanism of action by reducing the amount of gastric juice, increased pH, and free acidity. The antiulcer potential of both the extracts was attributed to the presence of flavonoids (quercetin) (Sharma et al., 2011a). Shanthi et al. (2011) developed an herbal capsule consisting of *A. marmelos* leaf powder exhibited significant anti-ulcer activity in Wistar albino rats. Antiulcer activity of AM extract at 200 and 400 mg/kg doses, revealed that the extract showed protection against aspirin induced ulcer symptoms such as increased ulcers, gastric volume, and free acidity. This study indicates *A. marmelos* leaves extract have potential anti-ulcer activity (Ashoka et al., 2012).

2.3.12 Anti-Stress and Antihistamine Activity

Anti-stress and apoptogenic activity of ethanolic extract of *A. marmelos* unripe fruits evaluated by using swim endurance and cold restrain stress in animal models (Duraismi et al., 2010; Sumanth and Mustafa, 2005). The

effects of Skimmianine (chemical constituent from roots of *A. marmelos*) on thapsigargin, ionomycin, DNP24-BSA and compound 48/80 induced histamine release from rat mast cells are tested in rat basophilic leukemia (RBL-2H3) and RPMCs. Docking results revealed that, Skimmianine strongly inhibited histamine release by acting on histamine H1 receptor from RBL-2H3 cells (Nugroho and Riyanto, 2010; Nugroho et al., 2011b).

The beneficiary effect of methanol extract of AM was evaluated for hypersensitivity and hemagglutination reactions in shed red blood cells antigen. The extract significantly enhanced the phagocytosis versus the control in a dose-dependent manner. Further, it was observed that the extract enhanced antibody-mediated and cell-mediated immune responses in rats (Ankur et al., 2010; Phatru and Syed, 2010). The anti-stress activity of *A. marmelos* was assessed by observing the change in the levels of stress hormone, non-enzymic antioxidants and glucose, in immobilization-induced stress in *in-vivo* experiment. The results indicated that the extract significantly reduced oxidative stress induced by immobilization in rat models (Anusha et al., 2013).

2.3.13 Protective Studies

2.3.13.1 Cardioprotective Efficacy

Traditional/ medicinal use of *A. marmelos* as cardioprotective drug was well documented in the literature (Dhiman, 2003; Purohit and Vyas, 2004; Parmar and Kaushal, 1982). Ethanolic extract *A. marmelos* unripe fruit was found to perform cardioprotective effect in isoproterenol (ISO) induced myocardial infarction and inferred that auraptene found as potent compound responsible for this activity (Veerappan et al., 2000). The extracts of *A. marmelos* were tested for cardioprotective roles and determined as potential cardiotonic drug using various biological models (Rajadurai and Prince, 2005; Maity et al., 2009). The cardioprotective effect of AM leaf methanolic extract was investigated against ISO induced myocardial damage in rats at two concentrations for a period of three weeks. Administration of AMLE significantly decreased activities of isozyme of Creatine kinase in serum and increased its concentration in heart tissue of animals at low and high doses. However, the extract at low dose did not exhibit any significant change in serum and tissue LDH activity than ISO control. Further, it enhanced the antioxidant enzymes and declined the higher concentrations of TBARS levels (Khanna et al., 2010).

The methanolic extract of *A. marmelos* leaves was evaluated for its cardioprotective potential against doxorubicin-induced cardiotoxicity. The extract notably reduced doxorubicin-induced higher levels of cardiac serum markers such as SGPT, SGOT, lactate dehydrogenase (LDH) and phosphokinase MB in a dose-dependent manner (Vishwakarma et al., 2018). Angiostatic efficiency of AM leaf extract was assessed using chick CAM (Chorioallantoic Membrane) assay. The leaf extract showed its mechanism of action by inhibiting the branch formation in blood vessels in developing CAM. Microscopic study results indicated that the leaf extract inhibited elongation and development of secondary/ tertiary blood vessels. It was reported that during inhibition there was no hemorrhage or any distortion in the blood vessels (Shah et al., 2014).

Cardioprotective effect of AM extract was investigated against the DOX-induced cardiotoxicity in mice. The extract significantly modulated DOX-induced NF- κ B activation, DNA damage and its cardioprotective activity topoisomerase-II enzyme activity. The extract further reduced free radical concentrations and enhanced antioxidant enzyme concentrations in treated animals (Jagetia and Venkatesh, 2015).

2.3.13.2 Hepatoprotective Effect

The hepatoprotective activity of *A. marmelos* leaf powder was investigated in alcohol-induced liver damage in albino rat models in 40 days experimental schedule. The crude powder exhibited noteworthy hepatoprotective activity against ethanol induced toxicity. The results concluded that the bael leaves powder have excellent liver protective activity (Singanan et al., 2007).

2.3.13.3 Cytoprotective Effect

The cytoprotective effect dried leaf powder of AM leaves was assessed in heavy metals treated freshwater fish (*Cyprinus carpio*). The results indicated that the AM leaf powder significantly protected cells in freshwater fish by enhancing the antioxidant system and by reducing membrane lipid peroxidation (Vinodhini and Narayan, 2009).

2.3.13.4 Radioprotective Studies

The radioprotective effect of hydroalcoholic extract AM was studied in Human peripheral blood lymphocytes exposed to different doses of γ -radiation was studied by Jagetia et al. (2003). While protective effect of AM fruit extract against radiation-induced lethality in mice was evaluated (Jagetia et al., 2004). Administration of *A. marmelos* leaf extract increased activities of the antioxidant enzymes SOD, CAT, and GSH peroxidase in normal mice as well as in diabetic rats (Tiku et al., 2004). Bone-marrow stem cells are more sensitive than intestinal crypt cells to the deleterious effects of ionizing radiation. However, as peripheral blood cells have a longer transit time than intestinal cells, the onset of a gastrointestinal syndrome occurs earlier than a bone-marrow syndrome (Jagetia and Venkatesh, 2005). Recently, traditional beverage standardized from *A. marmelos* fruits drink was and found to be rich in natural phenolic compounds, which were reported to have good antioxidant components (Abdullakasim et al., 2007). Protective effects of alcoholic extract of AM leaves against radiation-induced clastogenicity was investigated in mice models. The results indicated that the extract at 250 mg/kg body weight exhibited a noteworthy reduction in the levels of micronucleated polychromatic erythrocytes (Jagetia and Venkatesh, 2007).

Inhibition of lipid peroxidation is important in disease processes involving free radicals, and studies have shown that both leaf and fruit extracts prevented radiation-induced lipid peroxidation in the livers, kidneys, intestines, and spleens of mice. *A. marmelos* caused a concentration-dependent inhibition of H_2O_2 and iron-induced lipid peroxidation in mice brain homogenate. Radiation triggers an inflammatory response via mediators and activates significant physiologic and immunologic processes. Loss of immunity is associated with depletion of immunocompetent cells that can cause infection by opportunistic microbes. Immune activation is a protective approach, and immunostimulants enhance the overall immunity of a host by presenting a nonspecific immune response against microbial pathogens. AM leaf extract enhanced peritoneal macrophages and splenic lymphocyte counts in mice, suggesting it produces immunomodulatory effects (Baliga et al., 2010).

2.3.14 Antifertility Effect

Anti-spermatogenic activity of ethanolic extract of AM leaves was investigated in albino rats for a period of one-month experimental schedule. Administration AM leaf extract at 25 and 50 mg/ kg body weight significantly

reduced the sex organs weight, sperm count and enhanced the sperm motility, protein, and RNA content in male sex organs in dose-dependent manner indicated the anti-spermatogenic properties of the extract in albino rats (Sur et al., 1999).

The effect of water extract of AM leaves on spermatogenesis in male albino rats was evaluated in a 45 days experimental schedule. The extract showed a noteworthy reduction in testis, seminal vesicles, and epididymis (Sathiyaraj et al., 2010). A similar type of work was studied with methanolic extract of AM stem bark in male rats (Agarwal et al., 2010). The extract showed noteworthy infertility activity by reducing testis weight and testosterone levels. The extract further reduced sperm count, viability, and motility in male rats.

2.3.15 Analgesic Activity

Analgesic activity of extracts of the AM leaves was investigated in carrageenan-induced paw licking assay in Swiss mice. The extract exhibited notable analgesic activity by reducing the early and late phases of paw licking in treated animal models (Arul et al., 2005). Whereas analgesic activity of methanolic extract of AM leaves was assessed in acetic acid-induced withering and tail licking assay. The extract showed dose-dependent analgesic activity (Shankarananth et al., 2007).

2.3.16 Anti-Arthritis Activity

Arthritis reducing efficiency of methanolic extract of AM leaves were studied in collagen induced arthritis in Wistar rats for a period of 45 days. The extract markedly inhibited paw edema and arthritic index in collagen-induced animal group. Further, the extract significantly reduced rheumatoid factor in the treated group (Trivedi et al., 2011).

2.3.17 Anti-Inflammatory Activity

Anti-inflammatory activity of AM leaf extract was evaluated in carrageenan-induced paw edema and cotton-pellet granuloma in animal models. The extract significantly inhibited the carrageenan and cotton pellet-induced inflammation in treated animal models (Arul et al., 2005).

Similarly, the anti-inflammatory activity of AM unripe fruit pulp extracts was investigated in carrageenan-induced inflammatory animal models. Similarly, the anti-inflammatory activity of unripe fruit pulp and leaf extracts of AM was studied in carrageenan-induced inflammatory models. Pretreatment with both extracts significantly reduced inflammation in the tested animal models (Arul et al., 2004). Ghangale et al. (2008) studied the anti-inflammatory potential of AM aqueous extract in rat paw edema model. The extract shows promising anti-inflammatory activity against the tested animal models (Wistar albino rats). Bael leaf alcoholic extract antagonized the histamine-induced inflammation in guinea pig models. The extract demonstrated positive results in the above-studied models (Arul et al., 2005). In another study, bael showed strong and promising anti-inflammatory activity in acute and chronic inflammatory animal models (Benni et al., 2011).

2.3.18 Toxicity Studies

2.3.18.1 Toxicity Assay

Acute and subacute toxicity effects of water and methanolic extracts prepared from AM leaves was studied in Wistar albino rats. The toxicity results suggested that administration of the AM leaf extract from 50 to 100 mg/kg body weight for a period of 14 days did not exhibit any short term toxicity in male and female Wistar rats (Veerappan et al., 2007). While acute toxicity of ethanolic extract of dried fruit of AM was studied to evaluate its biosafety of crude extract. The results indicated that the extract at 2000 mg/kg body weight produced mortality of animals. But at lower concentration, the extract did not exhibit any signs of toxicity (1250 mg/kg body weight) (Joshi et al., 2009).

2.3.18.2 Antigenotoxic Activity

The substances which prevent toxic elements to damage the genetic material of the cell are called antigenotoxic agents. Antigenotoxic efficiency of AM methanolic extract was assessed against H_2O_2 and aflatoxin-induced toxicity. The extract significantly reduced H_2O_2 and aflatoxin-induced toxicity by suppressing the cytochrome P450 activity (Kaur et al., 2009).

2.3.19 Ameliorative Potential

The suppressive effect of AM stem bark hydroalcoholic extracts and its components para-coumaric acid, marmelosin, and umbelliferone was evaluated against neuroinflammation caused by vincristine in rat models. In results, it was found that the extract significantly attenuated inflammatory mediators in sciatic nerve and brain. Further, the extract enhanced the behavioral changes in treated animal models (Gautam and Ramanathan, 2019).

2.3.20 Anticonvulsant Activity

Anticonvulsant efficiency of the methanolic leaf extract of AM was assessed in PTZ-induced seizures in mice models at 100 and 200 milligram/kg concentration. The extract exhibited notable protection against PTZ-induced seizures, at 200 mg/kg concentration. It concluded that anticonvulsant activity of the extract attributed to the presence of flavonoids (Sankari et al., 2010).

2.3.21 Larvicidal Efficacy of Nanoparticles

Anti-inflammatory and larvicidal activity against three mosquito larvae of nickel NPs synthesized from AM crude leaf extracts tested using *in vitro* methods. The tested AM NPs exhibited enhanced anti-inflammatory and larvicidal activity (Angajala et al., 2014).

KEYWORDS

- 2,6-bis(1,1-dimethylethyl)-4-methyl
- *Aegle marmelos*
- isoproterenol
- nuclear factor- κ B
- rat basophilic leukemia
- TNF receptor

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CHAPTER 3

A Concise Review on Phytochemical and Pharmacological Studies of *Hybanthus enneaspermus* (L.) F. Muell

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3.1 INTRODUCTION

Hybanthus enneaspermus (L.) F. Muell. (Synonym: *Ionidium suffruticosum* Ging.; Basionym: *Viola enneasperma* L.) is a small suffrutescent herb of Violaceae. It is commonly called Spade Flower or Pink Ladies Slipper in English and Orithazh Thamarai in Tamil due to the large spade shaped pink anterior petal. It is also popularly known as Ratnapurush or Pursharathna in Sanskrit and Hindi due to its aphrodisiac property, especially to regain the lost strength for men. This plant is known to have several unique medicinal properties.

This plant is distributed in the tropical and subtropical regions of the world. It can grow up to 30 cm with many spreading or ascending branches. Stem woody at base, covered with scabs. Leaves sessile, linear-lanceolate or elliptic-lanceolate; base attenuate; margin distantly crenate; tip acute; stipules linear-lanceolate. Flowers solitary, axillary; pedicel slender. Sepals 5, subequal, lanceolate, acute. Petals 5, pink, unequal; lower one larger spade-shaped,

clawed, other 4 smaller, elliptic. Stamens 5. Ovary ovoid, 1-celled; ovules numerous; style clavate; stigma oblique. Capsules ovoid. Seeds many, ovoid.

3.2 BIOACTIVES

Hybanthus enneaspermus is reported to contain a variety of bioactive compounds which include dipeptide alkaloids, aurantiamide acetate, isoarborinol, β -sitosterol, triterpene, etc. Structure of some important phytochemical constituents are illustrated in Figure 3.1. Being a member of Violaceae, this plant is also reported to contain cyclotides, the cyclic mini-proteins.

Patel et al. (2013) gave a detailed review on phytochemistry and pharmacology of *H. enneaspermus*. Similarly, Baviya et al. (2015) and Rajasekar et al. (2016) also reviewed phytochemical and pharmacological aspects of this plant. Majumdar et al. (1979) isolated different phytochemicals from various parts of this plant. The compounds include: aurantiamide acetate, dipeptide alkaloids, isoarborinol, and β -sitosterol.

Through GC-MS analysis, Anand, and Gokulakrishnan (2012) separated seven phytochemicals from *H. enneaspermus*. These compounds are Propane, 1,1,3-triethoxy-, Phenol, 4,6-di(1,1-dimethyl)-2-methyl-, 1,14-Tetradecanediol, Phytol, 2-Pepridionne, N-[4-bromo-n-butyl]-, Cedran-diol, 8S, 14- and 2H-Pyran, 2-(7-heptadecyloxy) tetrahydro-. Retnam and de Britto (1998) separated various types of amino acids, sugars, and flavonoids from *H. enneaspermus* by paper chromatography. Several researchers conducted preliminary phytochemical screening which showed the presence of alkaloids, flavonoids, terpenoids, phenols, steroids, catechins, tannins, anthraquinones, sugars, and amino acids (Awobajo et al., 2009; Hemashenpagam and Praveena, 2010; Patel et al., 2011b; Amutha Priya et al., 2011; Remya Krishnan et al., 2012; Patel et al., 2013; Krishnamoorthy et al., 2014; Velayutham and Karthi, 2015; Thiyaga Raju et al., 2015; Anupa et al., 2016; Kavitha et al., 2017; Krupashree et al., 2018; Murugan and Kamaraj, 2018; Sheeba et al., 2019).

Retnam and de Britto (2003) isolated and identified five alkaloids, three flavonols, six steroids, and six terpenoids from *H. enneaspermus* through gas chromatography. The alkaloids include heteroxanthine, theophylline, theobromine, caffeine, and theacrine; flavonols include galangin, catechin, and kaempferol; steroids include agnosterol, dihydroagnosterol, dihydrositosterol, lanosterol, cholestanol, and cholesterol;

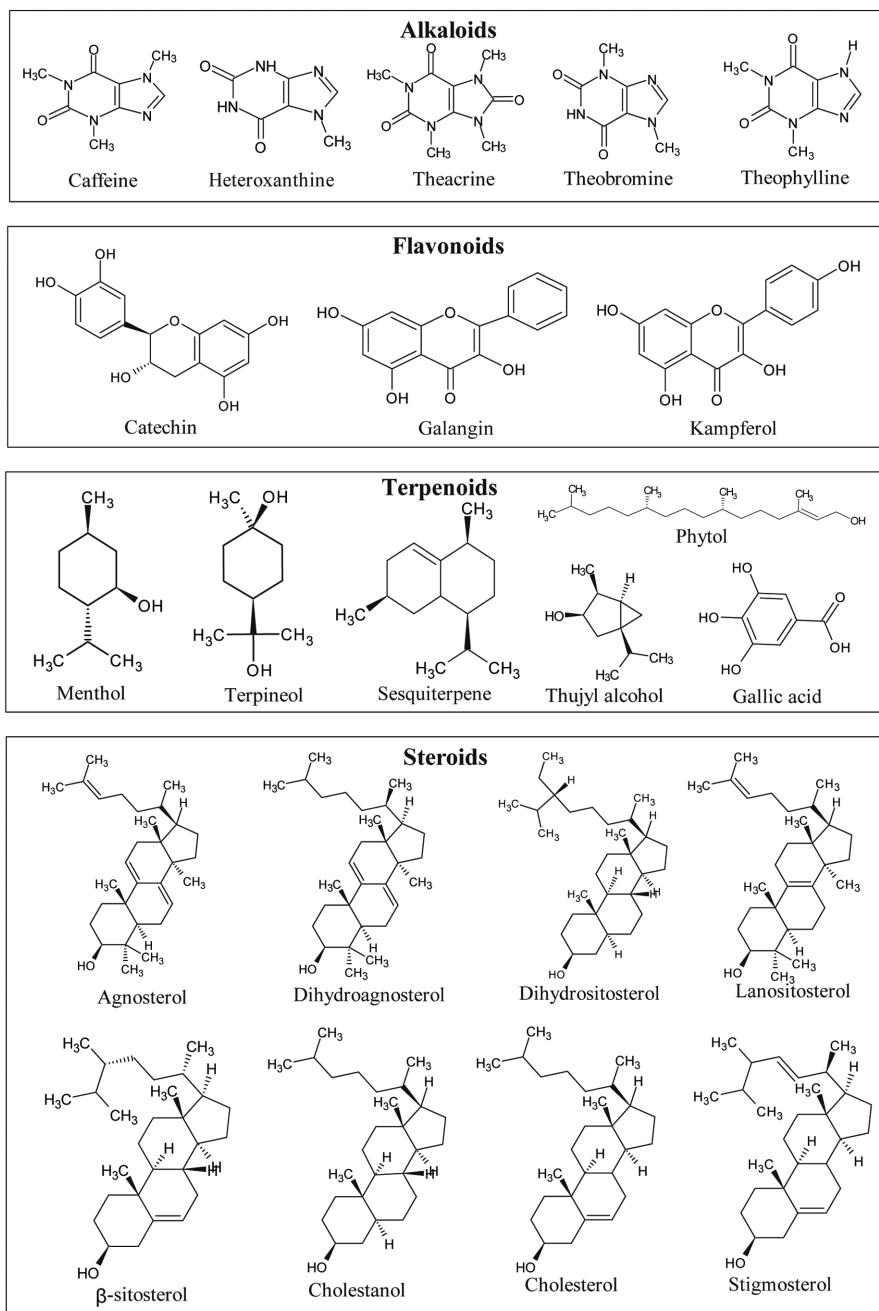


FIGURE 3.1 Some important phytochemical constituents present in *Hybanthus enneaspermus*.

and terpenoids include terpinol, menthol, sesquiterpene, gallic acid, thujyl alcohol and daucul.

Velayutham and Karthi (2015) obtained different peaks of GC-MS from the leaves of *H. enneaspermus*, determining the presence of phytochemical compounds and their therapeutic activities. The mass spectrum showed the presence of 16 different phytochemicals. Of these octadecanoic acid, phytol, vitamin E, bis-(2-ethylhexyl) phthalate, n-hexadecanoic acid, ethanone, dodecanoic acid, oxirane, etc., were the major compounds. They also compared these compounds with that of *in vitro* plants and also different fungal treated *in vitro* plants in their study. Krupashree et al. (2018) identified 41 compounds from the dried plant parts of *H. enneaspermus* through GC-MS of which the major therapeutic compound was stigmasterol covering 39.61% of peak area. Baviya et al. (2016) isolated active principles from the entire plant of *H. enneaspermus* using a variety of solvents through qualitative, quantitative, and chromatographic analysis. They quantified alkaloids, phenols, steroids, and flavonoids such as quercetin, rutin, gallic acid, thymoquinone, and gallangin from the extracts of ethyl acetate (EtOAc) and ethanol, but thymoquinone and gallangin were not found from the extracts of hexane and chloroform.

3.2.1 Cyclotides

Cyclotides are cyclic mini proteins characterized by less than 30 amino acids. They are plant-derived oligopeptides having a cyclic backbone and a cystine knot motif. Cyclotides have a variety of biological activities, especially their cytotoxic activity attracted significant attention for the potential anticancer applications.

Partial sequences of hyen A and hyen B were obtained from this plant and derived the sequences (Broussalis et al., 2001; Simonsen et al., 2005). Du et al. (2020) isolated and sequenced 12 cyclotides, namely, hyen C, hyen D, hyen E, hyen F, hyen G, hyen H, hyen I, hyen J, hyen K, hyen L, hyen M and cyO₂. Of the isolated 12 cyclotides, 11 cyclotides were novel and cycloviolacin O₂ is already known. Of the 11 novel cyclotides, hyen D, hyen E, hyen L, hyen M and cyO₂ demonstrated potent cytotoxicity. Hyen C comprises a unique sequence compared to other known cyclotides. Hyen D is the most abundant cyclotide in *H. enneaspermus*, having higher anti-cancer properties when compared to cycloviolacin O₂, a known cytotoxic cyclotide.

3.3 PHARMACOLOGY

3.3.1 Antimicrobial Activity

3.3.1.1 Antibacterial Activity

Sahoo et al. (2006,2008) showed antibacterial potentiality of *H. enneaspermus* using different extracts against six bacterial strains, namely, *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* by disc diffusion method. Among the different fractions, ethanolic extract was found to possess significant inhibitory activity compared to other extracts. The aqueous extract showed moderate effect, while chloroform extract and petroleum ether extract possessed less significant activity.

Retnam and de Britto (2007) separated 7 fractions of *H. enneaspermus* using column chromatography. These fractions were tested against two-gram positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus*; and five-gram negative bacteria, *Citrobacter freundii*, *Escherichia coli*, *Enterobacter aerogens*, *P. aeruginosa* and *Salmonella typhi*. Among these seven fractions, fraction 2 was active against two-gram negative bacteria, *E. aerogens* and *C. feundii* with 17 mm and 14 mm inhibition, respectively. Fraction 4 was active against one-gram positive bacterium, *B. subtilis* and two-gram negative bacteria, *E. aerogens* and *E. coli* with 14 mm, 15 mm, and 16 mm inhibition, respectively. The result showed that the plant had significant antimicrobial activity justifying its traditional use in treating different kinds of bacterial infections. Awobajo et al. (2009) showed the antimicrobial activity of methanolic leaf extracts of *H. enneaspermus* against *S. aureus*, *Citrobacter*, *E. coli* and *B. subtilis* and a fungus *Candida*.

Anti-microbial activity of aqueous and ethanolic extracts of *H. enneaspermus* was evaluated by Anand and Gokulakrsihnnanan (2012) against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *Shigella shigae*, *Salmonella typhi*, and *Proteus vulgaris* along with two fungal strains by using agar disc diffusion method and found that ethanolic extract was more active against these microbes than aqueous extracts. Vamsi and Bholla (2014) evaluated the antibacterial activity of this plant against *Enterococcus faecalis* and showed a mean inhibitory zone of 13 mm and noted the zone size increased with increase in concentration.

Murugan and Kamaraj (2018) reported antimicrobial activity of different extracts of *H. enneaspermus*. Petroleum ether extract showed maximum

zones of inhibition for *E. coli* when compared to other solvents, chloroform, methanol, and ethanol. Sheeba et al. (2019) isolated three endophytic fungi, namely, *Botrytis cinerea*, *Aschocyta pisi* and *Aspergillus nidulans* from the leaf and stem of *H. enneaspermus*. These endophytic fungal extracts showed antibacterial activity against 8 out of 10 bacterial strains. Of which *A. pisi* and *A. nidulans* showed maximum of 16 mm and 17 mm inhibition against *K. pneumoniae* and *E. coli*, respectively.

3.3.1.2 Antifungal Activity

Sahoo et al. (2007) tested the whole plant extracts of *H. enneaspermus* and showed the antifungal activity against three fungal strains, namely *Candida albicans*, *C. tropicalis*, and *C. krusei* and found that ethanolic extract showed a significant spectrum of inhibition when compared to other extracts. While petroleum extract showed moderate effect, chloroform and aqueous extracts showed less significant effect.

Arumugam et al. (2011) showed the antifungal activity of various extracts of *H. enneaspermus* against *Aspergillus niger*, *A. flavus* and *A. fumigatus* through disc diffusion assay. Of these extracts, methanol extracts showed maximum inhibitory effect followed by the extracts with petroleum ether and chloroform. Arumugam et al. (2012) showed the antifungal property of petroleum ether, chloroform, and methanol extracts of *H. enneaspermus* against *A. flavus*, *A. fumigatus*, *Candida albicans* and *C. tropicalis*. The methanol extract showed significant antifungal activity against all the fungal strains tested, followed by petroleum ether and chloroform extracts.

Anand and Gokulakrishnana (2012) reported the antifungal activity of ethanolic extracts of *H. enneaspermus* against *C. albicans* and *A. niger* by using disc diffusing method. In another study, the methanol and ethanol extract of *H. enneaspermus* showed maximum zone of inhibition (ZI) for *A. niger* and *A. flavus* when compared to petroleum ether and chloroform (Murugan and Kamaraj, 2018).

3.3.1.3 Antiviral Activity

Anbalagan et al. (2015) reported anti-HIV activity of the leaf extract by *in vitro* HIV-1 reverse transcriptase inhibition assay. They tested with methanol, ethanol, hexane, chloroform, and petroleum ether extracts and

observed positive result on methanol and hexane extracts. But no inhibition was observed on ethanol, chloroform, and petroleum ether extracts.

3.3.2 *Antioxidant and Free Radical Scavenging Activity*

Setty et al. (2007) showed the nephroprotective and free radical scavenging activities of aqueous and alcoholic extracts of *H. enneaspermus* in cisplatin-induced rat models. The antioxidant defense system was compromised, as indicated by the significant increase in TBARS levels and the decrease in GST, GSH, and SOD levels in renal tissues. The plant extracts were able to increase the decreased GST, GSH, and SOD induced by cisplatin and protect the kidneys from damage caused by lipid peroxidation. Alcoholic and aqueous extracts also showed a significant radical scavenging effect on free radicals DPPH, ABTS, superoxide, nitric oxide, and TBARS and ferric ion. The *in vitro* antioxidant activity of the hydroalcoholic extract of the leaves of *H. enneaspermus* has been reported by Roy et al. (2011) using the DPPH radical scavenging activity, hydrogen peroxide radical scavenging activity, reduction power activity and nitric oxide radical scavenging activity and observed a significant antioxidant activity of this plant.

Antioxidant activity of ethanolic extract of *H. enneaspermus* was determined by CAT, SOD, GST, GR, and LPO enzyme assays in paracetamol (PCM) induced mice. The toxicity of PCM tested in mice caused more serum transaminases, alkaline phosphatases and decreased levels of glutathione (GSH) in the liver, increased lipid peroxidation and antioxidant enzymes. However, the leaf of this plant extract regained the normal activities of enzymes by serving one of the plant products as an antioxidant for mouse serum and liver (Bhanu et al., 2011). Patel et al. (2011a) determined the total polyphenol and flavonoid contents from the alcoholic extract of *H. enneaspermus* and correlated with various antioxidant assays. The extract showed higher total antioxidant capacity, good reducing power and a significant scavenger of reactive oxygen species in addition to the presence of a higher phenolic content. According to them, significant antioxidant activity may be due to the presence of high phenolic content.

In another study, they also showed the antioxidant potential of four different fractions of *H. enneaspermus* in terms of total antioxidant dosage, DPPH dosage, reducing power, nitric oxide, and hydrogen peroxide. Of the four fractions tested, the EtOAc fraction exhibited a higher amount of antioxidant potential, a higher percentage of DPPH radical scavenging activity, nitric oxide, hydrogen peroxide, deoxyribose, and a higher reducing

power. They concluded from their study that the EtOAc fraction had a strong antioxidant potential compared to petroleum ether, chloroform, and aqueous fractions (Patel et al., 2011b). Thenmozhi and Premalashmi (2011) reported significant antioxidant activity and reduced lipid peroxidation activity in rat using hydroethanolic extract of *H. enneaspermus*. Amutha Priya et al. (2011) also evaluated the antioxidant potential of methanolic extract of *H. enneaspermus* by enzymatic and non-enzymatic methods. Enzymatic methods include superoxide dismutase (SOD), catalase (CAT), peroxidase, ascorbate oxidase and glucose-6-phosphate-dehydrogenase and non-enzymatic methods include, DPPH, superoxide scavenging, hydroxyl radical scavenging, reducing power, total phenol content and ascorbic contents. Based on the results, they concluded that methanolic extract possessed significant free radical scavenging activity.

Vuda et al. (2012) showed the antioxidant property of the aqueous extract of *H. enneaspermus* in CCl₄ induced rats. Pretreatment and post-treatment with an aqueous extract showed significant hepatoprotection by reducing the enzymatic activities of aspartate transaminase, alanine transaminase and alkaline phosphatase (ALP), and the levels of total bilirubin which had been increased by the administration of CCl₄. Pretreatment and post-treatment with an aqueous extract significantly lowered lipid peroxidation and the production of a corresponding increase in total tissue thiols in the liver. Ashok Kumar et al. (2013) determined the antioxidant activity of the aqueous extract of *H. enneaspermus* (= *I. suffruticosum*) by hydroxyl radical scavenging activity, FRAP assay and iron chelation activity. The IC₅₀ value of hydroxyl radical scavenging activity and FRAP were found to be 120 µg/ml and 430 µg/ml, respectively as against standard ascorbate at 410 µg/ml. The IC₅₀ value of iron-chelating was found to be 163 µg/ml as against the standard EDTA at 80 µg/ml. The aqueous extract showed significant free radical scavenging activity compared to standard drugs and was found to be concentration dependent.

Anish and Rajesh (2014) showed the antioxidant potential of field grown *H. enneaspermus* and compared with *in vitro* grown calli of this plant. The *in vitro* calli showed increased antioxidant activity than the field growth plants in all the free radical scavenging assays. Dab and Ragaven (2014) showed the free radical scavenging activity and cytotoxicity of hydroethanolic extract of *H. enneaspermus* at 500 µg/ml. Lycopene exhibited a significant amount (0.832 g) among the various antioxidants.

Various fractions of *H. enneaspermus* leaves were analyzed for antioxidant property by Thiyaga Raju et al. (2015) using DPPH as radical recipient. With the increase in the range of 250 to 1000 µg/ml of extract,

the antioxidant activity was found to be increased in all the extracts. The ethanolic extract showed relatively highest activity compared to other extracts. Anupa et al. (2016) determined the antioxidant activity of the ethanol extract of *H. enneaspermus* by DPPH, reducing power and hydrogen peroxide radical scavenging assays. The results showed that the maximum radical scavenging activity in DPPH was 24.32% versus 45.41% standard at 60 mg/ml. The reducing power assay showed a maximum absorbance of 1.038 at 60 mg/ml and in the hydrogen peroxide radical scavenging activity, the inhibition was 35.11%. Thus, the leaf extract has significant antioxidant activity and is used as a better source of natural antioxidants that could be useful in preventing the progression of oxidative stress.

3.3.3 Antidiabetic or Hypoglycemic Activity

Awobajo and Olatunji-Bello (2010) carried out hypoglycemic activity of aqueous and methanol leaf extracts of *H. enneaspermus* on normal and alloxan induced diabetic rats. Blood glucose levels after 12 hours fasting and after oral administration of plant extract were evaluated for 12 hours at 30 minutes interval. The aqueous and methanolic extracts of 80 mg/kg and 180 mg/kg body weight, respectively, were found to be effective hypoglycemic doses. This gave a percentage reduction of whole blood glucose level of 44.15 at 7 h and 44.94 at 10 h, respectively. The aqueous extract gave a hypoglycemic result similar to that of the standard hypoglycemic drug, glibenclamide.

Patel et al. (2011a) estimated the oral glucose tolerance and normoglycemic effect of different doses of alcoholic extract of *H. enneaspermus* peroral and hypoglycemic activity was tested at 250 and 500 mg/kg per oral per day for 21 days in streptozotocin (STZ) induced diabetic rats. The results showed significant rise in the body weight and fall in the blood glucose level on treatment with the alcoholic extract and increased glucose uptake compared to control group. Vennila and Pavithra (2015) evaluated the α -amylase and α -glucosidase inhibitory activity of various solvent extracts (ethanol, petroleum ether, aqueous, and acetone extracts) of *H. enneaspermus*. Ethanol extract showed maximum inhibitory effect for both α -amylase and α -glucosidase was observed on ethanol extract when compared to that of petroleum ether, aqueous, and acetone extracts.

3.3.4 Aldose Reductase Inhibitory Activity

Patel et al. (2012) showed the aldose reductase inhibitory activity of different fractions of *H. enneaspermus* for its potential use in diabetic cataract. The results showed a significant level of phenolics and flavonoids in EtOAc and aqueous fractions when compared to chloroform and petroleum ether fractions. Each fraction showed a significant difference in the aldose reductase inhibitory activity, and it was found to be the highest in the EtOAc fraction with an IC_{50} value of 49.26 $\mu\text{g/ml}$ followed by the aqueous extract with 70.83 $\mu\text{g/ml}$. The least inhibitory activity was observed in the petroleum ether fraction with IC_{50} value of 118.89 $\mu\text{g/ml}$, while moderate inhibitory activity was observed in the chloroform fraction with IC_{50} value of 98.52 $\mu\text{g/ml}$.

3.3.5 Antihyperlipidemic Activity

Vetriselvan et al. (2013) evaluated the anti-hyperlipidemic activity of hydroalcoholic extracts of *H. enneaspermus* on high fat diet-induced albino Wistar rat and observed the restoration of biochemical parameters altered by cholesterol. Treatment with three-doses of hydroalcoholic extracts (100, 200 and 400 mg/kg) and atorvastatin significantly reversed to normal. Among the three doses, the extract at a dose of 400 mg / kg was found to be more active. However, the activity was found to be lower than the standard atorvastatin administered at a dose of 1.2 mg/kg. The results indicated that the hydroalcoholic extract has a potential hypolipidemic effect on the restoration of liver functions.

3.3.6 Aphrodisiac Activity

Narayanaswamy et al. (2007) evaluated the aphrodisiac activity of ethanol and aqueous extracts of *H. enneaspermus* in sexually inactive male rats, both in a single dose and in chronic therapy over 28 days. They administered 300 mg/kg of both extracts and found that the aqueous extract in a single dose produced a decrease in assembly and intromission latency with an increase in the frequency of ejaculation and intromission. In the chronic model, alcohol, and aqueous extracts increased mount numbers, ejaculations, and intromissions with a decrease in assembly and intromission latency. Treatment with the plant extract also increased the level of testosterone in sexually inactive male rats. These results suggested that the plant may have aphrodisiac activity in sexually inactive male rats.

3.3.7 Anti-Infertility Activity

Anti-infertility activity of ethanolic extract of *H. enneaspermus* on endosulfan induced toxicity was evaluated by Nathiya and Senthamil Selvi (2013) in male albino rats. They evaluated various biochemical parameters in addition to sperm count and sperm motility. The plant extract recovered the infertility caused by endosulfan in male rats.

3.3.8 Analgesic Activity

Mozhi et al. (2013) screened the analgesic activity of ethanolic and petroleum ether extracts of *H. enneaspermus* using hot plate, tail immersion and tail-flick. The results showed that ethanolic extract was found to possess more analgesic activity than petroleum ether extract. They suggested that the analgesic activity may be due to the presence of phytochemical constituents, especially flavonoids and other polar constituents.

The analgesic activity of the aqueous extract of leaves of *H. enneaspermus* was studied by Aigbe et al. (2016) using acetic acid and acetylcholine-induced mouse writhing tests, formalin-induced pain tests and tail clamp tests in mice. The possible contribution of the CNS activity of the extract to its analgesic action was also evaluated by open-field and hexobarbital-induced sleep tests. The extract between 50 and 200 mg/kg significantly inhibited writhing in mouse writhing tests induced by acetic acid and acetylcholine. The analgesic effect was more effective at 100 mg/kg, producing 97.6% and 96.5% inhibition in the two tests, respectively. The extract also significantly increased the pain threshold in the tail clamp test and significantly reduced the reaction time in both phases of the formalin-induced pain test. The plant extract significantly reduced the locomotive and exploration activities of the mice in the field test, but produced no significant effect in the hexobarbital-induced sleep test in mice. These results showed that the aqueous leaf extract possesses analgesic activity mediated by mechanisms similar to those of opioid receptor antagonists, muscarinic receptor antagonists, and K⁺ channel opening.

3.3.9 Anti-Inflammatory Activity

Boomithan et al. (2004) evaluated the anti-inflammatory activity of methanol extract of *H. enneaspermus* (= *I. suffruticosam*) in acute models of rat hind paw edema induced by carrageenan, histamine, and serotonin.

The extract at doses of 200 and 400 mg/kg was found to have significant anti-inflammatory activity in the experimental models tested. The maximal anti-inflammatory activity at a dose of 400 mg/kg in all animal models and showed a 42.78% reduction in granuloma weight. The effect produced by the extract was similar to that of phenylbutazone, a prototype of a non-steroidal anti-inflammatory agent.

Tripathy et al. (2011) have shown the anti-inflammatory activity of alcoholic and aqueous extracts of *H. enneaspermus* against acute inflammation induced by carrageenan, histamine, and 5-HT (5-hydroxytryptamine) at doses of 250 and 500 mg/kg in rats. These extracts showed a decrease in paw edema in the animals tested in dose-dependent manner. The extracts also suppressed the inflammation induced by histamine and 5-HT. The alcoholic extract possessed a more significant activity when compared to the aqueous extract. Nandy et al. (2012) also showed the anti-inflammatory activity of this on carrageenin-induced paw edema in rats.

3.3.10 Anti-Arthritic Activity

Tripathy et al. (2009) showed the anti-arthritic activity of alcoholic and aqueous extracts of the whole plant of *H. enneaspermus* on Freund's adjuvant-induced arthritis (AIA) and found 12.8% and 10.6% yield on alcoholic and aqueous extracts, respectively. Both extracts significantly reduced paw thickness at the end of 30-day treatment. At the end of the study alcoholic extract showed more pronounce effect as comparable to aqueous extract.

3.3.11 Anti-Allergic Activity

Mozhi et al. (2013) screened the anti-allergic activity of *H. enneaspermus* by milk-induced eosinophilia and leukocytes methods using ethanolic and petroleum ether extracts. The results showed that the ethanolic extract has a greater anti-allergic activity than the petroleum ether extract.

3.3.12 Anticonvulsant Activity

Hybanthus enneaspermus has traditionally been used to treat epilepsy. Anti-convulsant activity of aqueous and ethanolic extracts of *H. enneaspermus* has been investigated by Hemalatha et al. (2003) using maximal electric

shock and strychnine-induced convulsion. The aqueous extract showed significant protection in both models at the doses of 200 mg/kg and 400 mg/kg. However, the ethanolic extract did not show protection in these models.

3.3.13 Antinociceptive Activity

Afolabi et al. (2014) showed the antinociceptive activity of ethanolic extract of *H. enneaspermus* in albino rats by tail dip and formalin test. Animals treated with doses of 500 mg/kg and 1000 mg/kg of extract showed increased tail-swab latency compared to animals treated with the standard drug, acetaminophen. In the formalin test, animals treated with a dose of 1000 mg/kg of extract significantly reduced paw licking time compared to acetaminophen.

3.3.14 Antitussive Activity

Boominathan et al. (2003) evaluated the coughing potential of methanol extract of *H. enneaspermus* (= *I.suffruticosam* Ging.) for its effect on a model of cough induced by sulfur dioxide gas in albino mice. The plant extract exhibited significant antitussive activity at the doses of 250 and 500 mg/kg (p.o.) showing 28.37% and 54.16% cough inhibition compared to the control group. The antitussive property of this plant is similar to that of codeine phosphate, a prototype cough suppressant.

3.3.15 Antiplasmodial and Larvicidal Activity

The effect of various solvent extracts of *H. enneaspermus* was tested *in vitro* for the antiplasmodial activity on the strains of *Plasmodium falciparum* K1 resistant to chloroquine and 3D7 sensitive to chloroquine. From the result, it was found that the methylene chloride extract exhibited a very significant inhibition, with an IC_{50} value of 2.57 μ g/ml against the tested strains (Weniger et al., 2004). Nazar et al. (2009) tested the extract of *H. enneaspermus* against *Culex quinquefasciatus* and showed significant larvicidal activity.

3.3.16 Anticancer and Cytotoxicity Activity

Though the ancient literature showed the anticancer property of *H. enneaspermus*, the scientific evidence is scarce. Due to the presence of anti-proliferating

agents through GC-MS studies, Jaikumar et al. (2017) evaluated and showed potent growth inhibitory activity against HEP-2 cell line (human epithelial cell line) with IC_{50} value of 19.75 $\mu\text{g/ml}$. They observed about 80% cytotoxicity of the leaf extract at a concentration of 100 $\mu\text{g/ml}$ against the viable HEP-2 cell line and concluded that this plant inhibited the proliferation of HEP-2 cancer cell line and showed toxicity with IC_{50} value of 19.75 $\mu\text{g/ml}$.

Dab and Ragavan (2014) studied the cytotoxic effect of hydroethanolic extract of *H. enneaspermus* on Hep2 Cell Lines by MTT assay. At the concentration of 5 mg/ml extract decreased the cell viability to 9.43% as against 100% in control. The result expressed that the cell viability was considerably decreased in a dose dependent manner.

3.3.17 Cardioprotective Activity

Radhika et al. (2011) reported the cardioprotective property of *H. enneaspermus* in rats induced by isoproterenol (ISO). Myocardial infarction was induced in rats by administration of ISO. The ethanolic extract in myocardial infarction induced rats reduced the oxidative stress by lowering oxidative lipids, reduced GSH, and normalized the levels of cardiac marker enzymes, namely, creatine kinase, lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase, serum glutamate pyruvate transaminase, and cardiac protein troponin I in histological studies.

3.3.18 Hepatoprotective Activity

Bhanu et al. (2011) showed the hepatoprotective nature of the ethanolic extract of *H. enneaspermus* on PCM-induced toxicity in mice. The hepatoprotective effect has been proven through blood serum and hepatic markers and liver histopathological studies. The leaf extract restored the normal activities of high lipid peroxidation and antioxidant enzymes and reduced the GSH content of the liver by serving one of the plant products as an antioxidant in mouse serum and liver. Due to the decreased lipid peroxidation in blood and liver, the plant product protects hepatocytes by breaking down necrotic cells in the liver.

The hepatoprotective and curative properties of aqueous extract of *H. enneaspermus* were studied in rats with hepatic lesions induced (CCl_4 - by Vuda et al., 2012). Rats were treated with aqueous extract at a dose of

either 200 or 400 mg/kg once daily for 14 days before CCl_4 intoxication and 2, 6, 24 and 48 h after CCl_4 intoxication. Pretreatment and post-treatment with the extract showed significant hepatoprotection by reducing the enzymatic activities of aspartate transaminase, alanine transaminase, and ALP as well as total bilirubin levels, which had been elevated by the administration of CCl_4 . Pretreatment and post-treatment with the extract significantly decreased hepatic lipid peroxidation as well as the production of a corresponding increase in total tissue thiols. Post-treatment with an aqueous extract improved ceruloplasmin levels. The histopathological examination of rat liver sections treated with an aqueous extract confirms the biochemical observations in the serum.

3.3.19 Nephroprotective Activity

Setty et al. (2007) showed the nephroprotective activity of alcoholic and aqueous extracts of *H. enneaspermus* in cisplatin-induced rat models. They observed that cisplatin-induced renal injury, which was evidenced by a decrease in kidney function in experimental animals. The administration of alcoholic extract in dosages of 250 and 500 mg/kg and aqueous extract in dosages of 500 mg/kg body weight normalized the increased blood urea, blood protein, and serum creatinine. These extracts protected the kidneys from damage due to lipid peroxidation and increased body weight. The alcoholic extract was found to be more effective than the aqueous extract.

3.3.20 Neuroprotective Activity

Kar et al. (2010) reported the CNS activity of ethanolic and aqueous extracts of *H. enneaspermus* in model mice by maze test (plus, Y-maze), sleep time induced by barbiturates and alcohol, suspension tail test, desperation test, head dipping test, locomotor activity and motor coordination test. The extracts were administered orally to mice with doses of 250 and 500 mg/kg. Diazepam 1 mg/kg, chlorpromazine 5 mg/kg, and imipramine 30 mg/kg have been administered intraperitoneally as standard drugs. In all tests, animals treated with *H. enneaspermus* extract showed significant activity compared to animals treated with standard drugs.

KEYWORDS

- *Hybanthus enneaspermus*
- *Ionidium suffruticosum*
- isoarborinol
- phytochemical
- β -sitosterol
- violaceae

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CHAPTER 4

Chemical Characterization and Pharmacology of *Gnetum africanum*

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4.1 INTRODUCTION

Gnetum africanum, which belongs to the family of Gnetaceae is a leafy greenish climbing vegetable that is mostly found in Angola, Congo, Nigeria, Gabon, Asia, and South America tropical regions. In Africa, *Gnetum buchholzianum* and *Gnetum africanum* are the two main prevalent species (Ali et al., 2011). It is commonly called Okazi or Afang leaf in Nigeria. This green leafy vegetable is an indispensable part of our diet and contributes immensely to the well-being of the human race. Different countries use the edible leaves to prepare different recipes and cuisines ranging from stew and soups by cutting them into small strips. For instance, the leaf is used to prepare vegetable or edikang ikong soup, egusi soup and oha soup in Nigeria. The *G. africanum* tree is not usually planted but grows normally as a forest vine that its leaves are collected as forest vegetables for medicinal and culinary purposes (Ali et al., 2011). They are different varieties of *G. africanum*; Asutan, Oron, Ikom, Welw, and Koko varieties.

4.2 CHEMICAL CHARACTERIZATION OF *GNETUM AFRICANUM*

The standard for assessing the nutritional value of plants includes their protein composition in amino acids and their lipid contents in fatty acids.

The antioxidant, vitamin, and mineral contents which is used to evaluate most tropical plants as a good source of nourishment for the body were also taken into account.

4.2.1 *Phytochemical Screening*

Phytochemical screening of the leaves of *G. africanum* by Njoku et al. (1997) revealed the presence of tannins, saponin, flavonoids, alkaloids, and glycosides. Mensah et al. (2008) also detected alkaloids, and tannins in the plant leaves, but these authors did not detect the presence of saponin in the *G. africanum* leaves. Ouabonzi et al. (1983) identified certain glycosylflavones while working with the extract from *G. africanum* leaves. Ouabonzi et al. (1983) also believed that flavone-O-glycosides are the major and distinctive flavonoids present in *G. africanum*.

Many phenolic compounds, such as trimeric stilbenes, flavonostilbenes, and flavones have been isolated and identified in various varieties of *G. africanum* (Edet et al., 2005). While working on the polar fraction of *G. africanum* stem extracts, Iliya et al. (2002a, b) isolated stilbene glucosides, flavonostilbenes, and dimeric stilbenes. Iliya et al. (2002a) isolated from the stems of *G. africanum* two stilbenes dimers, termed gneaffricanins A and B, and bisisorhapontigenin with eight already known stilbenoids. Iliya et al. (2002b) detected the presence of four new stilbenes dimers, termed gneaffricanin C, D, E, and F, with four known stilbenes from *G. africanum* stems. Iliya et al. (2003) isolated from the polar fractions of acetone extract of the stem lianas of *G. africanum* three non-existing stilbenes, termed gnemonoside H, I, and J with nine already known stilbenoids. Phytochemical analysis of *G. africanum* by Okerulu and Onyema (2015), showed the presence of alkaloids, glycosides, saponins, and tannins while flavonoids, sterols, and phenols were absent. Qualitative and quantitative phytochemical analysis by Iiodibia et al. (2015) showed that both the ethanolic and aqueous stem and leaf extracts of *G. africanum* contained alkaloids, tannins, flavonoids, saponins, phenols, terpenoids, sterol in varied quantities except cyanogenic glycoside.

The results of phytochemical screening of *G. africanum* by Akin-Osanaiye et al. (2019) showed that steroids, saponins, and tannins were present in both hexane and methanol extracts while flavonoids, alkaloids, glycosides, and carbohydrate were absent in both fractions. Studies by Ezekwe et al. (2020) on qualitative phytochemical screening of the aqueous leaf extract of *G. africanum* revealed the presence of saponins, terpenoids, tannins, flavonoids, steroids, phenols, cardiac glycosides and alkaloids.

4.2.2 Proximate Analysis

The proximate analysis of *G. africanum* leaves showed that the plant is rich in fiber, protein, minerals, fat, and carbohydrate content (Ali et al., 2011). The work by Okerulu and Onyema (2015) on proximate analysis of *G. africanum* showed a moisture content, crude protein, crude lipid, ash content, carbohydrate, and crude fiber of 10.9%, 20.12%, 2.70%, 6.70%, 52.39% and 7.10% respectively.

4.2.3 Mineral Analysis

Akpanabiatu et al. (1998) reported that soup made from *G. africanum* when compared with soups made from other plants, is rich in calcium, iron, magnesium, copper, phosphorus, and zinc. The research work by Okerulu and Onyema (2015) on comparative assessment of elementary composition of *G. africanum* showed the presence of sodium, magnesium, calcium, iron, zinc, manganese, potassium, and copper in order of decreasing concentration. The criteria for determining the nutritional value of plants refer to their protein composition in amino acids and lipid composition in fatty acids. The mineral, vitamin, and antioxidant contents for which most tropical plants are known as a good source are also taken into account.

4.2.4 Amino Acid Profiling

It is seen as an abundant source of protein, especially for its high essential amino acids content. Amino acid profiling of *G. africanum* by Eyo et al. (1983) showed an abundant source of essential amino acids (leucine, isoleucine, methionine, lysine, threonine, phenylalanine, tryptophan, and valine) and nonessential amino acids (serine, aspartic acid, proline, glutamic acid, glycine, cysteine, alanine, tyrosine, arginine, and histidine).

4.2.5 Physiochemical Properties

Njoku et al. (1997) isolated yellow oil from the powdered dry leaves of *G. africanum*. On treatment with n-hexane solvent, the physiochemical properties of the oil revealed low acid value and peroxide value but the saponification value, iodine value, unsaponifiable material, β -carotene, β -sitosterol, and

phospholipids are high (Edet et al., 2005). These components also protect the oil from rancidification by oxidation.

4.2.6 Fatty Acid Analysis

Analysis of the fatty acid content of the plant oil by Njoku et al. (1997) revealed the presence of unsaturated fatty acids such as Myristic acid C14:0, Palmitic acid C16:0 15.75, Palmitoleic acid C16:1 2.69, Stearic acid C18:0 5.34, Oleic acid C18:1 9.85, Linoleic acid (x6) C18:2 8.70, Linolenic acid (x3) C18:3 3.84, Arachidic acid C20:0 5.17, Arachidoleic acid C20:1 2.73 and Behenic acid C22:0 1.66.

4.2.7 Gas-Chromatography/Mass Spectrometry Screening

According to Edet et al. (2005) the main components of the volatile oil are β -caryophyllene, (E)-phytol, β -selinene, and (E) β -ionone. Trace amounts of other compounds were detected in the essential oil of *G. africanum* include α -pinene, trans- β -damascenone, camphene, valencene, α -zingiberene, 7-epi- α -selinene, γ -cadinene, and methyl palmitate. The GC-MS Analysis by Ezekwe et al. (2020) revealed 14 compounds of which caffeine, n-Hexadecanoic acid, 2-methoxy-4-vinylphenol, tetradecanoic acid, cyclopentaneundecanoic acid and 2 cyclopenten-1-2 hydroxy were most prominent.

4.2.8 Antinutrient Analysis

Studies by Isong et al. (1999) revealed the presence of antinutrients such as hydrocyanic acid, oxalate, tannins, glucosinate, and phytic acid in *G. africanum* at levels below the toxicity threshold. Another work by Fokou and Domngang (2003) showed that tannins complicated the bioavailability of proteins while glucosinate inhibited the uptake of iodine, iron, and calcium for the three varieties of *G. africanum* at a low concentration.

Udosen and Ukpanah (1993) research showed that phytic acid reduced the bioavailability of minerals such as iron, calcium, zinc, and phosphorus by forming complexes that are not readily hydrolyzed by the enzymes in the intestine and that are insoluble. Studies by Ekop (2007) and Udosen and

Ukpanah (1993) showed that most antinutrients are eliminated and destroyed during processing and cooking.

4.3 PHARMACOLOGY

4.3.1 Antimicrobial Activity

Antibacterial and antifungal studies on the ethanolic and aqueous leaf and stem extracts of *G. africanum* showed that it inhibited the growth of the microbes tested in a dose dependent manner (Ilodibia et al., 2015). Moderate inhibitory effect of the essential oil of *G. africanum* was observed by Edet et al. (2005) on the growth of *Escherichia coli* (minimal inhibitory concentration, 39 mg/mL). According to the research by Akin-Osanaiye et al. (2019), both stem and root of *G. africanum* had dose-dependent antimicrobial effect on *S. aureus* with maximum inhibitory zones of 17.50 mm and 16.00 mm at 500 mg/ml for methanol and hexane extracts.

4.3.2 Anti-Inflammatory Activity

Studies in the Republic of the Congo showed that *G. africanum* treated inflammatory related sicknesses such as hemorrhoid, boil, to soothe pains and dressing for warts (Besong et al., 2001). In Nigeria, research by Edet et al. (2005) on *G. africanum* leaves revealed its potency in the treatment of sore throats, enlarged spleens, and also as cathartic.

4.3.3 Antioxidant Activity

Research by Iliya et al. (2003) on antioxidizing power of the stilbenes in *G. africanum* showed high antioxidant activity. Antioxidant studies by Ebenyi et al. (2020) revealed that treatment of oxidative stressed rats with ethanol extract of *G. africanum* increased the activities of the antioxidant enzymes GR, CAT, and SOD in a dose-dependent manner. *In vitro* antioxidant studies by Ezekwe et al. (2020) showed that the DPPH scavenging ability of *G. africanum* leaf extract (43.2, 60.5, 68.8, and 75.7) was significantly high in comparison with the standard drug (81.1, 82.6, 85.1, and 90.4).

4.3.4 Anti-Carcinogenic Activity

Ebenyi et al. (2020) studies on the effect of ethanolic leaf extract of *G. africanum* on testosterone and Estradiol induced benign prostate hyperplasia showed a decrease in the level of malondialdehyde (MDA), ACP, and PSA on rats administered with the extract in a dose-dependent manner.

4.3.5 Anti-Hyperglycemic Effect

The work of Tandu-Umba (1995) revealed that *G. africanum* high fiber content was used to control blood sugar levels in diabetics and ease constipation. The result of Udoh et al. (2012) studies on the effect of extract of *G. africanum* on lipid and lipoprotein profiles in rats showed that ingestion of the extract increased the serum levels of High density, low density, total cholesterol, triglycerides, and LDL-cholesterol positively. Studies by Udeh et al. (2018) revealed an increase in weight for rats administered with *G. africanum*.

4.3.6 Antianemic Properties

Silas et al. (2017) showed that the leaf extract of *G. africanum* increased the hematological parameters Hb, Hct, RBC, and TWBC in Wistar rats. A study performed by Udeh et al. (2018) on the hematological profile of Wistar rats following chronic oral administration of *G. africanum* showed a higher level of red blood cell count as compared to the control.

4.3.7 Gastroprotective Effect

Sandrai et al. (2020) work on the effect of *G. africanum* on peptic ulcer treated in rats showed a significant increase in pH value and a decrease in gastric volume.

4.3.8 Endocrine Function

Activity of ethanolic extract of *G. africanum* leaf by Udoh (2012) on endocrine functions in female rats showed a dose-dependent decrease in serum

levels of follicle-stimulating hormone (FSH), progesterone, and an increase in luteinizing hormone (LH), estrogen (Es) and no alteration in prolactin level. This finding suggests that the ethanolic extract of *G. africanum* is a phytoestrogen that can be formulated pharmaceutically to form a contraceptive for females.

4.3.9 Antivenom Properties

Studies by Edet et al. (2005) stated that *G. africanum* is used as an antidote for treatment of certain types of poisons and as a remedy for nausea.

KEYWORDS

- estrogen
- follicle-stimulating hormone
- *Gnetum africanum*
- luteinizing hormone
- antimicrobial activity
- phytochemical

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CHAPTER 5

Bioactives and Pharmacology of *Uvaria chamae* P. Beauv.

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5.1 INTRODUCTION

Medicinal plants have been used for centuries to ensure the well-being of populations. There are a significant number of medicinal molecules obtained from plants used in traditional medicine (Newman and Cragg, 2012). *Uvaria chamae* is one of them. Of the class Magnoliopsida and Annonaceae family, it is a small tree up to 4 meters high. The tree is used locally, being harvested in the wild for its edible fruits, medicinal, and other uses (Monon et al., 2015). *U. chamae* is found throughout West Africa: in the bas-cavally region of Côte d'Ivoire, in Benin in the Plateau where it is called "ayadaha." It is disseminated in the coastal savannahs of Guinea and Sudan (Eyog Matig et al., 2001; Guillaumet, 1967). In the South of Benin (West Africa), *U. chamae* is one of the plants most used in the traditional treatment of salmonellosis by herbalists (Dougnon et al., 2018). This review focuses on the pharmacological properties and chemical composition of *U. chamae*. It aims to provide an overview of the chemical and pharmacological potential of the plant for an optimal valuation.

5.2 BIOACTIVES

The chemical characterization of the medicinal plant revealed the presence of cardiac glycosides, tannins, flavonoids, alkaloids free and combined Anthraquinones, and cyanogenic glycosides from *Uvaria chamae* (Oluremi et al., 2010; Adejumo et al., 2010). Several cytotoxic agents have been isolated from *U. chamae*. Uvaretin and isouvaretin, have been isolated from the stem bark of *U. chamae* and their structures have been established as C-benzylflavanones (Hufford et al., 1976). Chamuvarinin (with an adjacent bis-tetrahydrofuran ring and a tetrahydropyran ring), desacetylurvaricin, quamocin, and neoannonin were also isolated from the roots of *U. chamae* (Fall et al., 2004). Acetogenins are also found in the organs of *U. chamae*. Cis-bullatencin has been isolated from the cyclohexanic extracts of the roots (Fall et al., 2002), while the seeds contain joolanin (Fall et al., 2006). Uvarinol, a cytotoxic tribenzylated flavanone have also been isolated (Hufford et al., 1979).

Alkaloids such as arnepavine, racem O,O-dimethylcoclaurine, nornantenine, nantenine, and corydine have been isolated (Philpov et al., 2000). Uncommon o-hydroxybenzylated flavanones and chalcones: diuvaretin, isochamanetin chamanetin, isouvaretin, dichamanetin, and uvaretin have been isolated (Kongstad et al., 2015).

In the category of volatile constituents, root, and leaf bark oils are characterized by a predominance of sesquiterpenes and aromatic compounds, respectively. In leaf oil, -cadinene is mainly found. On the other hand, in the root oil, it is rather benzyl benzoate and thymoquinoldimethyl which are the major components (Ogunimei et al., 1989). Another major compound of leaf oils is germacrene while the major constituents of the root bark oil were methoxylated derivatives of p-cymene and benzyl benzoate (Figures 5.1) (Ayedoun et al., 1999).

5.3 PHARMACOLOGY

5.3.1 Antiviral Activity

U. chamae roots extracts were active on herpes simplex virus (HSV) type 1 at 50 µg/ml (Silva et al., 1997). *U. chamae* root and stem bark extracts demonstrated significant *in vitro* anti-measles virus activity with IC₅₀ 1.216 µg/mL and 3.281 µg/mL, respectively (Oluremi and Adeniji, 2015).

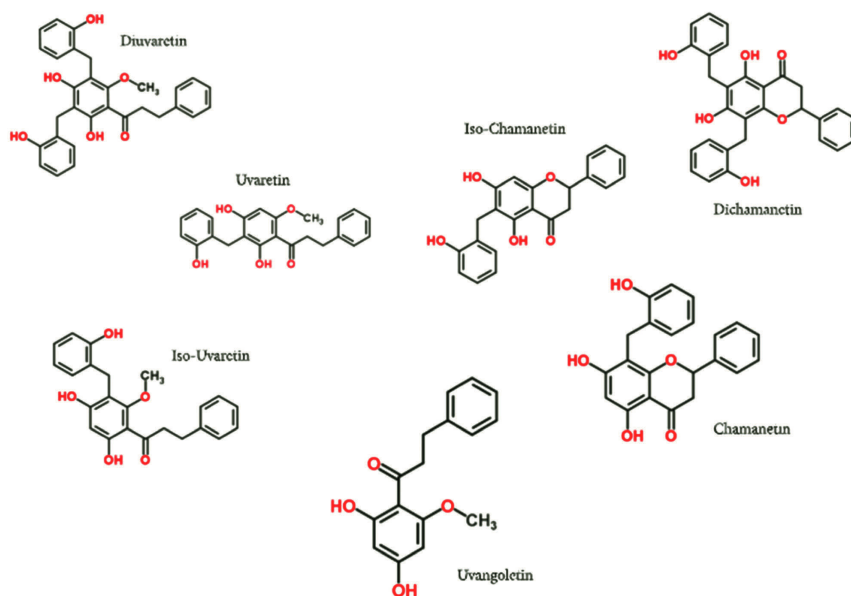


FIGURE 5.1 Dihydrochalcone compounds from *Uvaria chamae* roots (Reprinted with permission from Koudokpon et al., 2018. <https://creativecommons.org/licenses/by/4.0/>)

5.3.2 Antibacterial Activity

Cold and hot water extracts *U. chamae* inhibited the growth of *Staphylococcus aureus* and *S. pyogenes*. Cold or hot ethanol extracts of *U. chamae* inhibited the growth of *S. aureus*, *S. pyogenes*, *Escherichia coli*, *Pseudomonas aeruginosa* and *S. typhi* (Ogbulie et al., 2007). Stem bark extract inhibited the growth of Methicillin-resistant *S. aureus* (MRSA), *S. aureus*, *E. coli*, *Klebsiella* spp., *Proteus* spp., and reference strains *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC27853 (Oluremie et al., 2010). In some work, the activity of certain sub-fractions of the methanolic extract of stem bark were more active than chloramphenicol and penicillin G (Ebi et al., 1999). The growth of *E. coli*, *S. aureus*, and *P. aeruginosa* were inhibited by crude ethanolic extract of the root bark and leaves (Ogueke et al., 2007). Ethanolic extract of *U. chamae* roots presented bactericidal effect against *E. coli* sensitive, *Shigella* sp., *S. flexneri* ESBL and *E. coli* ESBL (Monon et al., 2015). Vancomycin-resistant enterococcus (VRE) and MRSA strains were all sensitive to ethanol root extract. It was possible to identify, by ion mobility mass spectrometry, 10 dihydrochalcone and chalcone responsible for the antimicrobial activity of *U. chamae* (Koudokpon et al., 2018).

A study performed in Benin showed that aqueous extract of leaves of *U. chamae*, at 400 and 200 mg/L, is active on *Salmonella* spp. and *Salmonella typhimurium* ATCC 14028 in chicks. No toxicity was noted (Legba et al., 2020).

5.3.3 Antifungal Activity

U. chamae have antifungal activity. Crude methanolic extracts of leaves and roots inhibited *Candida albicans* (Om et al., 2012). *U. chamae* extract inhibited the fungal plasma membrane (PM) H⁺-ATPase (Kongstad et al., 2015).

5.3.4 Antioxidant Efficacy

A study performed in Ivory Coast showed that aqueous and ethanol extracts of *U. chamae* roots have antiradical activities against DPPH with IC₅₀s between 3.52±0.38 and 14.35±4.86 µg/ml. The ethanolic extract of *U. chamae* showed significant high antioxidant activity (4.02 ± 0.50 g/ml) than aqueous extract (12.59 ± 2.77 g/ml) (Monon et al., 2015). The seed extracts have also a good antioxidant activity. Ethanolic seeds extract also inhibited DPPH and ABTS radicals (IC₅₀ = 34.3 and 29.6 g/mL). In this study, aqueous seed extract of *U. chamae* had the best activity with IC₅₀= 23.5 g/ml (Ita et al., 2017).

5.3.5 Hepatoprotective Activity

Aqueous extracts of *U. chamae* at 0, 100, and 1000 mg/kg of body weight did not produce acute toxicity in Sprague Dawley rats. In 28 days subchronic oral toxicity study, no observed adverse effect level' was established for the extract (Olumese et al., 2016). Root bark ethanol extract exhibited an anti-hepatotoxic effect greater than that of silibinin. Thus, this extract could be useful in the development of more active antihepatotoxic agent (Madubunyi et al., 1996). Otherwise, a study showed that oral administration of the methanol root bark extract (60 mg/kg) significantly reduced pentobarbitone-induced sleep after acetaminophen poisoning of rats. Considerable protection (up to 92%) against acetaminophen cytotoxicity was noted by pretreatment with the extract. This protection is greater than that conferred by silibinin (89.6%). (Madubunyi, 2012).

5.3.6 Anti-Hyperglycemic Effect

U. chamae induced significant reductions in weight, plasma glucose levels, low density lipoprotein and cholesterol, in diabetic rats. The extract, at 400 mg/kg, 250 and 100 bodyweight reduced glucose at 86.02, 81.50 and 85.16, respectively (Emordi et al., 2016). Another study showed that the root extract of *U. chamae* has hypoglycemic properties. 250 and 500 mg/kg body weight of the extract showed a significant reduction in blood glucose levels at 2 h and 6 h compared to control (Emeka et al., 2015). It is demonstrated that the antidiabetic effects of *U. chamae* roots ethanol extract may be through increased insulin secretion and -amylase and -glucosidase inhibition (Emordi et al., 2018).

5.3.7 Antimalarial Activity

Oral administration of 300,900 mg/kg day of the ethanolic root extracts of *U. chamae*, inhibited *Plasmodium berghei-berghei*. The activity is comparable to that of the chloroquine at 5 mg/kg day (Okokon et al., 2006). In a chloroquine-resistant *P. berghei* experiment, the combination (methanol extracts of the leaf of *U. chamae* at 400 mg/kg and amodiaquine at 10 mg/kg [UCL400+AQ10] mg/kg) gave a chemosuppression of 45.80%, significantly lower than 78.40% (AQ) (Adepiti and Iwalewa, 2016).

5.3.8 Anti-Ulcer Activity

In a study performed in Nigeria, the leaves ethanolic extracts of *U. chamae* had an interesting anti-ulcer activity on Wistar rats. This activity was superior to that of cimetidine. Induction of the ulcer was carried out using indomethacin, histamine, and stress models (Chilaka et al., 2010).

5.3.9 Cardioprotective Activity

U. chamae roots extracts showed a cardioprotective effect via an increase in HDL-cholesterol levels (Emrdis et al., 2018).

5.3.10 Trypanocidal Effects

U. chamae root bark ethanol extract showed a significant trypanocidal effect that can be compared with that of diminazene aceturate. Parasitemia reduction was dose-dependent in mice infected with *Trypanosoma brucei-brucei* (Madubunyi et al., 1996).

5.3.11 Antivenom Properties

U. chamae methanol leaves extract neutralized some biological effects of *Naja nigricollis* venom. The plant extract has an inhibition on the physiological parameters, exaggeratedly increased by the venom (James et al., 2013). The author of the study concluded that it can be an alternative or complementary treatment strategy of envenomation by *N. nigricollis*.

KEYWORDS

- **annonaceae**
- **anthraquinones**
- ***Uvaria chamae***
- **methicillin-resistant *S. aureus***
- **molecules**
- **plasma membrane**
- **vancomycin-resistant enterococcus**

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CHAPTER 6

Essential Oil of *Trachyspermum ammi* (L.) Sprague ex Turrill-Phytochemistry and Therapeutics

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6.1 INTRODUCTION

Trachyspermum ammi (L.) Sprague ex Turrill [Syn. *Trachyspermum copticum* link or *Carum copticum* (L.) link] is a well-known medicinal plant that belongs to the family Apiaceae. It is commonly known as ajwain, ajowan, carom or Bishop's weed. The plant is an annual, aromatic, erect herb (30–70 cm height) bearing white flowers and small brownish fruit. The seeds are small, gray with bitter taste. The stem contains many branches, small feather-like leaves, 4–12 rays of flower heads with 6 to 16 flowers in each head (Bairwa et al., 2012). *T. ammi* is supposed to originate in the Eastern Mediterranean region, probably in Egypt, while reported to be widely spread throughout the regions of India, Iran, Pakistan, Iraq, and Afghanistan. Although, the plant is reported to grow in saline soil however optimum soil pH for its growth ranged between 6.5–8.2 with temperature 15–25°C and relative humidity 65–70%. The best harvesting time for *T. ammi* is reported to be the end period of winter or earlier duration of spring (Hassanshahian et al., 2014). The plant is enriched with various medicinal values such as antifungal, anti-inflammatory, antihypertensive, antiviral, nematicidal, antiparasitic, and

anthelmintic properties. The fruit of *T. ammi* is reported to have vast therapeutic properties and is generally used as primary treatment for different gastrointestinal problems such as indigestion, flatulence, colic pain, etc. Moreover, the specific aroma of plant contributed to its vast historical role as spice and condiment to enhance flavor, color, and aroma of diet along with having efficacious therapeutic attributes (Gradinaru et al., 2018). The biological activity is mainly attributed to the essential oils accumulated primarily in Fruits (up to 5%). The presence of essential oil is responsible for its odor and taste.

6.2 BIOACTIVES

Fruits or seeds of *T. ammi* is considered to be highly nutritious or therapeutically enriched part of the plant. The analysis of the herb showed the presence of fiber, moisture, protein, fat, carbohydrates, minerals, thiamine, riboflavin, nicotinic acid, carotene, alkaloids, flavonoids, tannins, saponins, and glycosides (Duke, 1992; Qureshi and Kumar, 2010). The characteristic odor and taste of *T. ammi* is due to the presence of essential oil, accumulated mainly in fruit/seed. In most of the studies, the major components of essential oil were thymol and carvacrol among phenols and p-cymene and γ -terpinene among non-phenols (Nagalakshmi et al., 2000; Pruthi, 1992). The typical flavor of the essential oil is due to the presence of thymol and carvacrol.

Chatterjee (1995) isolated camphene, carvacrol, p-cymene, dipentene, myrcene, α - and β -pinenes, phenol, α - and β -pllelandrenes, γ -terpinene, thymine, thymol, linoleic, oleic, palmitic petroselinic acid and resin acids from fruits. The essential oil from fruit possessed styrene, α -pinene, β -pinene, myrcene, p-cymene, γ -terpinene, thymol, and carvacrol (Mohaghghzadeh et al., 2007). The seed essential oil showed the presence of thymol (40%), p-cymene (15.6%), γ -terpinene (11.9%), carvacrol (5%), β -pinene (4%), limonene (4%), camphene, and myrcene as observed by gas chromatography-mass spectrometry (GC-MS) analysis. However, in another study, the oil obtained from aerial parts of plant contained p-cymene (14.08%), thymol (12.96%), isothymol (51.20%), g-terpinene (6.79%) and limonene (11.89%) as the prime bioactive components (Kambouche and El-Abed, 2003). Similarly, the GC-MS analysis of fruit essential oil showed the presence of 8 compounds where cymene (76.27%) was identified as the major component followed by thymol (13.30%), DL-limonene (3.23%), 1,8-cineole (2.58%) and γ -terpinene

(1.68%) (Kedia et al., 2015). In most of the studies, it has been well established that the chemical composition of *T. ammi* changes according to plant parts, geographic location, age of plant, method of extraction, etc. Isothymol (50%) was reported to be a major bioactive component followed by p-cymene, thymol, limonene, and γ -terpinene in the *T. ammi* seed EO collected from Algeria. Similarly, thymol (98%) was also reported as a major bioactive of *T. ammi* EO from south India. However, Farooq et al. (1993) reported slight variation in EO bioactive component composition in *T. ammi* leaf EO having composition of thymol (5%), camphor (3%), cadinene (43%) and longifolene (11%). Dwivedi et al. (2012) reported petroselinic acid as the major component of the fixed oil from the seeds in India. Further, Chahal et al. (2017) analyzed variation in bioactive components of *T. ammi* EO from different geographical region and reported the presence of different phytochemical constituents such as thymol, p-cymene, γ -terpinene, α -pinene, β -pinene, α -thujene, myrcene, α -carvacrol, β -selinene, trans-sabinene, β -phellandrene, terpinene-4-ol, hydrate linalool, terpinolene, and limonene. The methanolic extract of seeds showed 25 compounds, including two new aromatic glucosides and two glucosides (Ishikawa et al., 2001), whereas the acetone extract of the same showed thymol (39.1%) as the major component while several others such as p-cymene (1.6%), palmitic acid (1.6%), oleic acid (10.4%), xylene (0.1%), linoleic acid (9.6%) and g-terpinene as minor components (Singh et al., 2004). Garg (1998) isolated 6-O- β -D-glucopyranosyloxythymol, a glucoside from seeds. Lockwood et al. (2002) in their study showed the presence of 41 compounds including cadinol (10.6%), elemol (11.5%), limonene (2.4%), cadinene (7.8%), humulene (2.0%), muurolol (4.9%), eudesmol (3.0%), elemene (3.9%), muurolene (2.6%) and caryophyllene (6.2%) from the dichloromethane extract of cell suspension culture of *C. coticum* (Figure 6.1).

6.3 PHARMACOLOGY

6.3.1 Antiviral Activity

T. ammi seed essential oil exhibited 80% and 40% inhibition to Japanese encephalitis virus at 0.5 mg/ml concentration by plaque reduction neutralization test method in pre and post-exposure treatment, respectively (Roy et al., 2015).

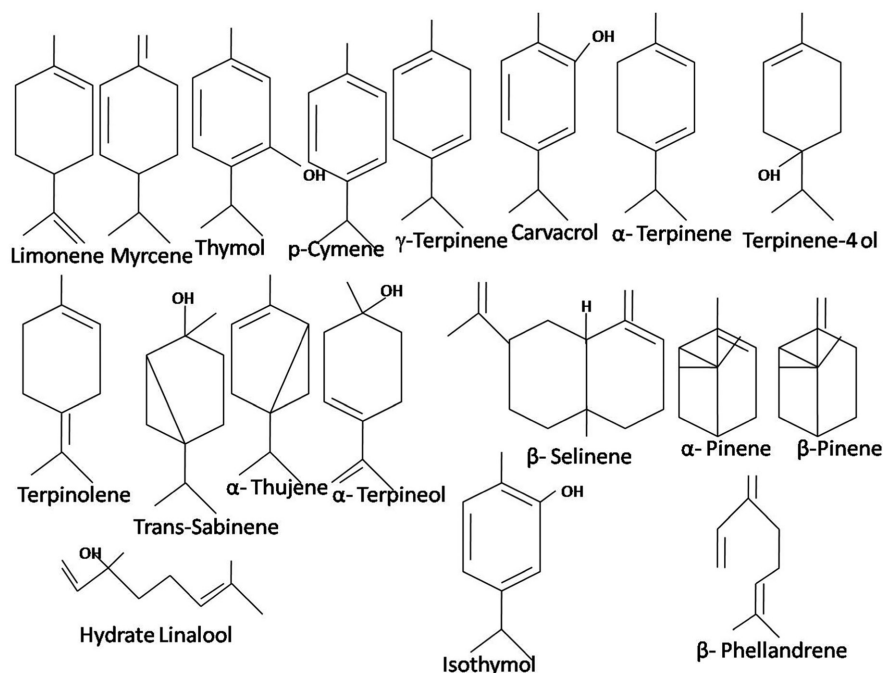


FIGURE 6.1 Structures of some major bioactive constituents of *T. ammi* essential oil.

6.3.2 Antibacterial Activity

Ethanol and acetone extract of *T. ammi* seeds was active against a number of bacteria. The ethanol extract showed significant antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bordetella bronchiseptica*, *Klebsiella pneumonia*, *S. epidermidis*, *E. coli* and *Bacillus pumilus* whereas acetone extract showed activity against *Shigella flexneri*, *E. coli*, *S. aureus*, *P. aeruginosa*, *Salmonella typhi*, *K. pneumonia*, *S. typhimurium* and *Enterococcus faecalis* (Shahidi, 2004; Kaur and Arora, 2008; Masih et al., 2012).

The essential oil exhibited significant antibacterial activity against both gram positive and gram-negative bacteria, including *E. coli*, *Proteus vulgaris*, *K. pneumoniae*, *S. aureus*, *B. subtilis* and *B. megaterium* (Hassan et al., 2016). Further, the seed essential oil was found toxic against antibacterial drug-resistant strains of *K. pneumoniae*, *E. coli* and *S. aureus* isolated from urine culture of hospitalized patients at 100–250 $\mu\text{g/ml}$ concentration (Hassanshahian et al., 2014). The oil showed pronounced

antibacterial activity against plaque forming oral bacteria with mean minimum inhibitory concentrations (MIC) of 250, 125, 250, and 125 µg/ml, respectively for *Streptococcus mutans*, *S. oralis*, *Lactobacillus acidophilus* and *L. fermentum*. The MIC values were higher as compared to chlorhexidine gluconate (CHX) (gold standard) but statistically significant (Dadpe et al., 2018). The antibacterial activity of essential oil against a wide range of bacteria may be due to the presence of large amounts of thymol or carvacrol, the phenolic compounds. These studies suggest the potency of seed essential oil to be developed as a natural antibacterial agent in pharmaceutical industries.

6.3.3 Antifungal Activity

Seed ethanol extract was reported to have promising antifungal activity against *Penicillium* sp., *Aspergillus niger*, *A. flavus*, *A. ochraceus*, *A. oryzae* and *Fusarium moniliforme* (Odhav et al., 2002). The essential oil from seed also has broad fungitoxic spectrum against a wide range of fungi including *Alternaria tenuissima*, *A. niger*, *A. oryzae*, *D. tetramera*, *A. ochraceus*, *F. moniliforme*, *F. graminearum*, *P. citrium*, *Cochlostyla ovoidea*, *P. madriti*, *Acrophialophora fusispora*, *C. lunata*, *F. chlamydosporum*, *F. poae*, *A. flavus*, *Myrothecium roridum*, *Papulaspora* sp., *A. grisea*, *P. viridicatum*, *Rhizoctonia solani* and *Cheilomenes lunata*, (Dwivedi and Singh, 1998; Thangam and Dhananjayan, 2003). Kedia et al. (2015) reported a broad spectrum of fungal toxicity of fruit essential oil as it caused 100% growth inhibition of 19 major food spoiling fungal species at 0.8 µl/ml concentration. The possible cause of this activity is the strong activity of thymol due to the presence of a phenolic OH group. Further, thymol when mixed with cymene (another major component of oil), enhances its antimicrobial activity. The study also suggests the primary target organelle is the fungal plasma membrane (PM) leading to ergosterol synthesis inhibition and ions leakage from the fungal cells. This study based on findings recommended the application of *T. ammi* fruit essential oil for complete protection of food items against food spoiling fungi.

6.3.4 Anti-Mycotoxigenic Activity

Kedia et al. (2015) tested antiaflatoxigenic activity of *T. ammi* fruit essential oil and its components cymene, thymol, DL-limonene, 1,8-cineole and

γ -terpinene. The minimum aflatoxin inhibitory concentration for oil and thymol was reported at 0.6 and 0.1 $\mu\text{l/ml}$ concentration, respectively, while the other components showed poor activity. The findings suggest that the overall activity of oil was due to the synergistic effects of its components as cymene, the main component showed the poorest activity while thymol showed the strongest activity. In another study, *T. ammi* oil showed complete antiaflatoxicogenic activity at 0.5 and 0.75 $\mu\text{l/ml}$, respectively from *A. niger* and *A. flavus* (Gemedu et al., 2014). The seed aqueous extract showed up to 65% degradation of aflatoxin G1 while the dialyzed extract was capable to degrade >90% of the toxin (Velazhahan et al., 2010). In a similar study, Iram et al. (2016) evaluated aqueous extract of seeds and leaves for their ability to detoxify aflatoxin B1 (AFB1) and B2 by *in vitro* and *in vivo* assays. The results showed significant action of seeds extract (92.8 and 91.9% for AFB1 and AFB2, respectively); however, the leaves extract showed poor activity.

6.3.5 Insecticidal Activity

The *T. Ammi* essential oil showed pronounced insecticidal activity against a wide range of insects when analyzed through different parameters. The seed essential oil and its main component, thymol depicted strong larvicidal, repellent activity, vapor toxicity as well as oviposition-deterrent efficacy against the malarial vector, *Anopheles stephensi* (Pandey et al., 2009). The fruit essential oil showed potent repellent activity and reported to inhibit and caused deformities in different developmental stages of wheat flour insect pest *Tribolium castaneum* along with also inhibiting its oviposition potential (Chaubey, 2007).

6.3.6 Nematicidal Activity

The *T. ammi* essential oil showed strong nematicidal activity against Pinewood nematode, *Bursaphelenchus xylophilus* (LC_{50} value 0.431 mg/ml) (Park et al., 2007). Choi et al. (2007) investigated the nematicidal activity of oil components α -pinene, camphene, β -pinene, myrcene, limonene, γ -terpinene, terpinen-4-ol, thymol, and carvacrol against Pinewood nematode and found thymol and carvacrol the most effective ones. The study confirmed the nematicidal activity of oil due to the activities of thymol and carvacrol.

6.3.7 Anti-Filarial Activity

Mathew et al. (2008) reported significant activity of the crude methanolic extract and the active fraction of *T. ammi* fruit against adult bovine filarial *Setaria digitata* worms through applying both MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] and worm motility reduction assays. The active principle of *T. ammi*, i.e., 2-isopropyl 5-methyl phenol was further analyzed for its *in vivo* antifilarial activity against the human filarial worm *B. malayi* and reported to have potent filaricidal activity in terms of causing female worm sterility.

6.3.8 Antioxidant Activity

The presence of carotenoids such as β -carotene, lutein and flavonoids make *T. ammi* a powerful antioxidant agent. Bajpai and Agrawal (2015) evaluated the antioxidant potential of seed extract by the scavenging assay and nitric oxide radical scavenging assay. At 200 $\mu\text{g/ml}$ concentration, the extract inhibited H_2O_2 up to 70.04% and nitric oxide radical up to 72.80% whereas at the same concentration, the ascorbic acid showed 94.96% inhibition. Mazumder et al. (2014) exhibited antioxidant property of ethanol extract of oil through 2, 2-diphenyl-1-picryl-hydrazyl (73.41%), nitric oxide (67.33%), superoxide (63.22%), hydroxyl radical scavenging assay (62.48%) and lipid peroxidation ability in bovine brain extract (69.22%). The fruit essential oil showed strong free-radical-scavenging activity through DPPH assay in a dose-dependent manner, and the IC_{50} value (0.467 $\mu\text{l/ml}$) was found superior to some of the earlier reported essential oils and synthetic preservatives (Kedia et al., 2015). Chatterjee et al. (2013) tested *in vitro* antioxidant potency of *T. ammi* essential oil by DPPH, H_2O_2 radical scavenging activity and ferric reducing antioxidant power (FRAP) assays and the values were compared with ascorbic acid. The result showed high, good, and moderate activities of FRAP, DPPH, and H_2O_2 radical scavenging assay suggesting the oil as a possible bioresource of antioxidants to be used in food and pharmaceutical industry.

6.3.9 Anti-Inflammatory Activity

The alcoholic and aqueous seed extract at 100 mg/kg doses showed significant anti-inflammatory activity in acute rat model and a sub-acute rat model.

The data obtained in carrageenan induced rat paw edema and cotton pellet induced granuloma was found closer to Aspirin and phenylbutazone, the synthetic anti-inflammatory agent (Thangam and Dhananjayan, 2003).

6.3.10 Analgesic and Anti-Nociceptive Activity

Dashti-Rahmatabadi et al. (2007) evaluated the analgesic and anti-nociceptive effect of fruit ethanolic extract and compared with morphine by using a tail-flick analgesiometer device. Within 2 h post-drug application, it produced significant increase in tail-flick latency (TFL). The authors suggested that this type of antinociceptive action may be of the opioid type. Hejazian (2006) carried out an experimental trial to compare the anti-nociceptive effect of total essential oil with morphine sulfate using formalin test. The results showed an anti-nociceptive effect on both early and late phases. In another study, the essential oil significantly reduced the neuropathic feet burn compared to placebo under a randomized controlled placebo-control clinical trial (Petramfar et al., 2013).

6.3.11 Hepatoprotective Activity

Srivastava et al. (1999) in their study depicted the hepatoprotective, bronchodilator, antihypertensive, and antispasmodic activities of the aqueous-methanol extract of seeds. The extract at 3–100 mg/kg dose caused a dose-dependent arterial blood pressure (BP) fall in anesthetized rats. The extract at 0.1–3.0 mg/ml dose caused a repressive effect on the K^+ induced contractions in isolated rabbit aorta and jejunum preparations. The extract at 0.1–1.0 mg/ml dose inhibited carbachol and K^+ induced bronchoconstriction in isolated guinea-pig tracheal preparations. The extract at 500 mg/kg dose forbade paracetamol (PCM) and carbon tetrachloride-induced rise in serum alkaline phosphatase (ALP) and aminotransferases in rats. Further, *T. ammi* is also reported to maintain the normal level of liver enzymes against CCl_4 -induced liver damage in mice, suggesting its efficient hepatoprotective attribute.

6.3.12 Hypotensive Activity

The methanolic seed extract of *T. ammi* is reported to have the hypotensive effect that causes a dose-dependent lowering of BP from 6 to 42% at a dose

of 3 and 100 mg/kg, respectively (Gilani et al., 2005). Bradycardiac or hypotensive effect of *T. ammi* is due to its bioactive constituent thymol, which has the property to block calcium channel.

6.3.13 Antitussive and Bronchodilatory Activity

Boskabady et al. (2005) evaluated the clinical effect of aerosols of aqueous and macerated seed extracts, carvacrol, codeine, and saline by counting the number of coughs produced. The result showed significant suppression in cough numbers from both the extracts suggesting their antitussive activity. Boskabady et al. (2007) tested the bronchodilatory effect of decocted extract on the asthmatic patient's airways in a trial study and found that the extract showed bronchodilatory effect as compared to the effect of theophylline.

6.3.14 Anti-Lithiasis Activity

In a human study, *T. ammi* seeds were decocted in milk and orally provided to volunteers suffering from urinary stone for 9 days. The results were found satisfactory against pure Ca-oxalate stone (Sabar, 2010).

6.3.15 Antidiabetic Activity

T. ammi oil at 4 μ l/ml concentration exhibited strong α -amylase (88.55%) and α -glucosidase inhibitory activity (89%) comparable to that of acarbose (90.96 and 91.67% respectively for α -amylase and α -glucosidase). The oil has raised the glucose uptake in L6 myotubes in a dose dependent manner suggesting its anti-hyperglycemic activity that may further be used as an antidiabetic agent (Aneesa et al., 2019).

6.3.16 Digestive Stimulant Activity

T. ammi has been recommended as a digestive stimulant and antifatulent agent by traditional practitioners since long back. The aqueous extract has been proved to be an enhancer of gastric juice, activities of several digestive enzymes and bile juice which ultimately leads to solve several gastric problems (Vasudevan et al., 2000). However, in a study, *T. ammi* showed

teratogenicity in rat fetuses and hence not advisable to intake during pregnancy (Nath et al., 1997).

KEYWORDS

- blood pressure
- ferric reducing antioxidant power
- gas chromatography-mass spectrometry
- tail-flick latency
- *Trachyspermum ammi*
- *Trachyspermum copticum*

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CHAPTER 7

Biomolecules and Therapeutics of *Pimpinella tirupatiensis* N.P. Balakr. & Subr. (Family: Apiaceae)

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7.1 INTRODUCTION

Pimpinella tirupatiensis (Adavikothimera) is a critically endangered and endemic medicinal plant found only in the Seshachalam hills of India's Eastern Ghats. The phytochemistry and pharmacology of *Pimpinella tirupatiensis* were reviewed in depth by Narasimhulu et al. (2012).

7.2 PHYTOCHEMICAL CONTENTS OF *PIMPINELLA TIRUPATIENSIS*

In the previous few decades the *P. tirupatiensis* has been subjected to intensive chemical investigations as a result of its high healthful worth. Few reports have been published regarding the phytochemical content of *P. tirupatiensis*. Few reports are revealed concerning the phytochemical content of *P. tirupatiensis*. Venkata Raju and Bakshu (2002) have with success known compounds from the foundation volatile oil of *P. tirupatiensis* like 3-methyl-5-pyrazolone (1.3%), 3-pentene-2-one (3.2%), camphene (1.6%), borneol (0.5%), menthone (1.1%), cis-carveol (6.7%), D-3-Carene (8.9%), geranyl acetate (0.3%), nonalactone (3.4%), 1-nonanol (0.5%), methyl geranate (4.3%), β -cedrene (0.7%), neral (1.3%), β -bisabolene (3.2%), β -bisabolene (9.2%), geranyl hexanoate (0.8%), citronellyl acetate (1.5%), elemol (5.8%), nerol (1.1%), β -bisabolol (0.8%), trans-cadinol (0.8%), β -cadinol (4.4%) and phytol

(1.2%) (Figure 7.1) Vijay et al. (2011) detailed the separation of compounds from ethanolic rough extricate of *P. tirupatiensis* leaf, presence of 2-butyl-1-octanol (1.36%), 1-(1,5-dimethyl-4-hexenyl)-4-methyl- (4.41%), eugenol (3.64%), decanal (2.69%), 5-(1,5dimethyl-4-hexenyl)-2-methyl (4.52%), α -farnesene (1.25%), 1-methyl-4-(5-methyl-1-methylene-4-hexenyl)-(S)- (synonyms:-Bisabolene) (2.47%), 3-(1,5-dimethyl-4-hexenyl)-6-methylene (4.00%), cyclohexene, tetradecanoic acid (1.22%), 1,3-cyclohexadiene, cyclohexene, 1,6,10-dodecatrien-3-ol, 3,7,11-trimethyl (2.70%), Spiro (4.5) dec-6-en-8-one, L-Serine, O-(phenylmethyl)- (3.42%), 9,12-Octadecadienoic acid (Z,Z)- (12.19%), α -cedren-9- β -ol (3.55%), gingerol (28.8%) undecanoic acid (3.48%), 1,7-dimethyl-4-(1-methylethyl)- (2.15%), n-hexadecanoic acid (12.86%), oleic Acid (2.55%) and heptacosane (2.66%) (Figure 7.2). Sudhakar et al. (2011) carried out preliminary phytochemical test for hexane, benzene, chloroform, and alcohol extract of the drug and reported the presence of alkaloids, flavonoids, indoles, leucoanthocyanins steroids, carbohydrates, phenols, steroidal nucleus, proteins, lignins, tannins, saponins, terpenoids, methylenedioxy functional compounds and coumarins. Devi et al. (2013) reported that the highest amount of polyphenols content was observed in ethanolic extract of *P. tirupatiensis* (1.44 ± 0.04) at 800 μ g of extract. Sirisha and Sujathamma (2018) carried out a phytochemical test of aqueous, chloroform, petroleum ether and benzene extract of *P. tirupatiensis* leaves, stem, and root tuber and reported the presence of alkaloids, flavonoids, glycosides, tannins, saponins, and sterols in high concentrations.

7.3 PHARMACOLOGICAL PROPERTIES OF *PIMPINELLA TIRUPATIENSIS*

7.3.1 Antimicrobial Activity

Jeevan Ram et al. (2004) reported that the ethanolic concentrates of *P. tirupatiensis* displayed different levels of inhibitory movement against human pathogenic microorganisms like *Pseudomonas aeruginosa*, *M. roseus*, *Micrococcus luteus*, *Staphylococcus aureus* (bacterial strains) and *Candida albicans* (parasitic endure) various focuses.

The antimicrobial activity of different concentrations (50 to 150 g/mL) of *P. tirupatensis* leaf extracts in various solvents (acetone, methanol, ethyl acetate (EtOAc), chloroform, and hexane) was evaluated against pathogenic bacterial strains (*Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Proteus mirabilis*, *Bacillus*

subtilis, and *Proteus vulgaris*) (Ranjit et al., 2016). They reported that methanol and EtOAc leaf extracts of *P. tirupatiensis* in *in vitro* showed maximum inhibitory effect against *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*, but no activity against *Salmonella typhimurium* and *Proteus vulgaris* among the bacterial strains.

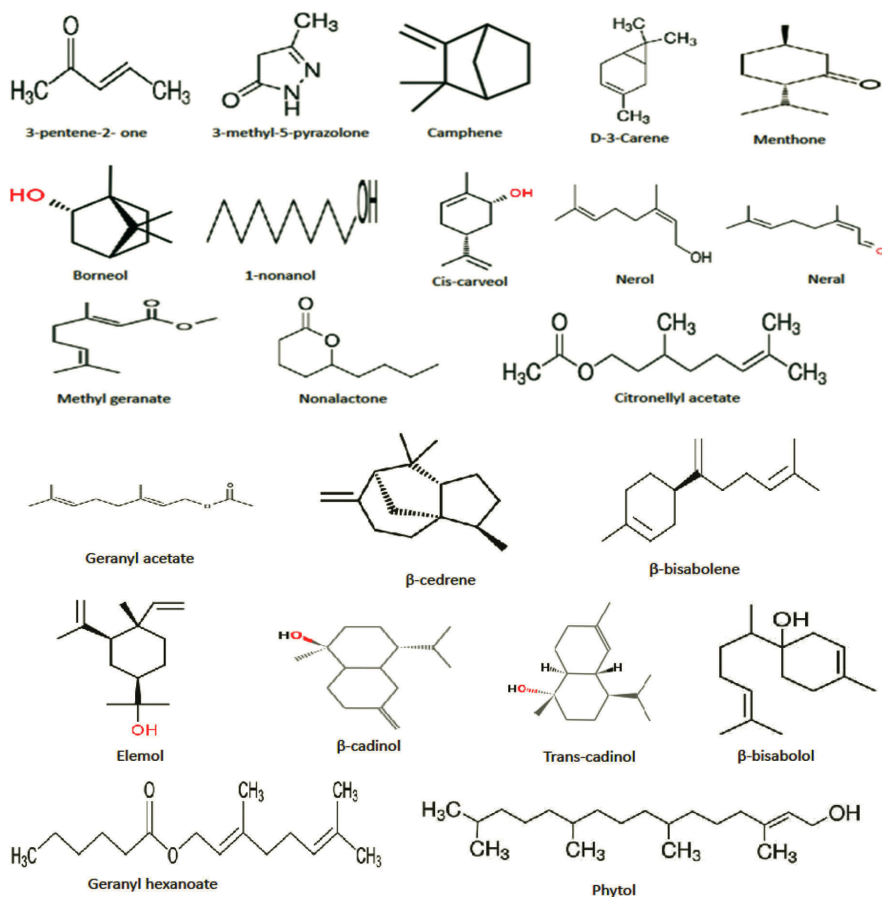


FIGURE 7.1 Essential oil compounds from *P. tirupatiensis* root (Venkata Raju and Bakshu, 2002).

7.3.2 Antioxidant Activity

Palani et al. (2009a) found that treatment with an ethanol extract of *P. tirupatiensis* greatly improved the decreased levels of antioxidant enzymes

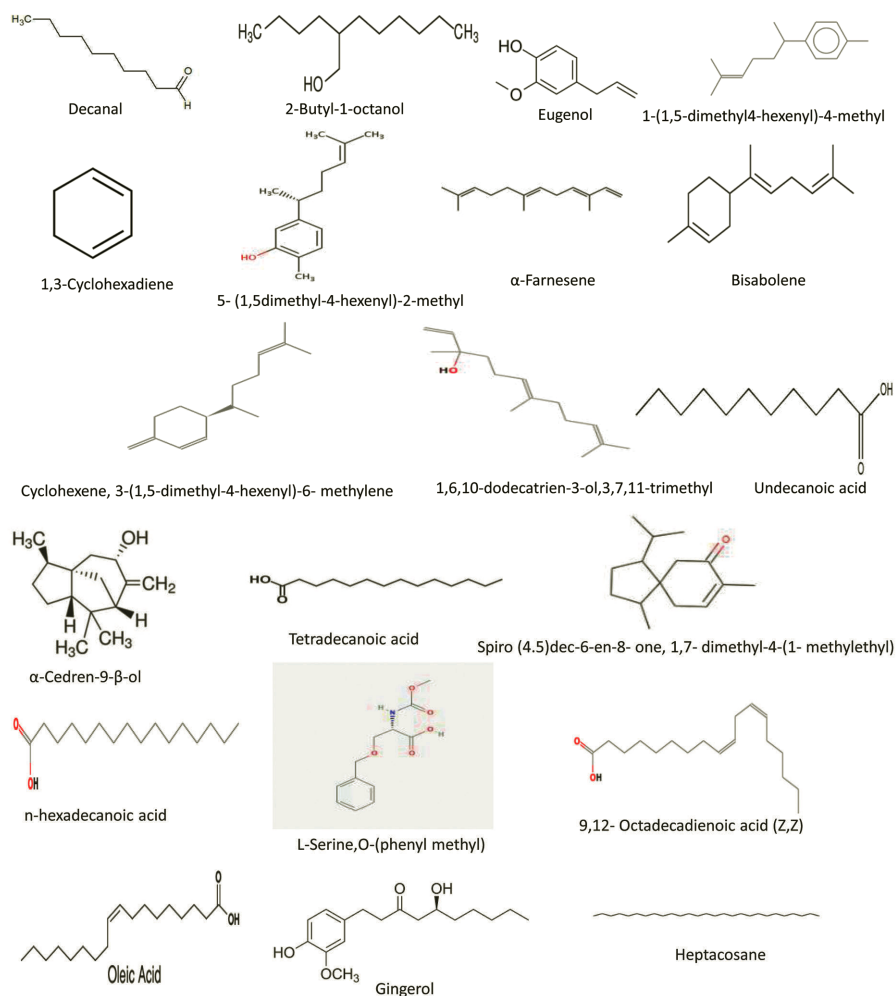


FIGURE 7.2 Phytochemical compounds from ethanolic crude extract of *P. tirupatiensis* leaf (Vijay et al., 2011).

(superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) peroxidase, and glutathionyl-transferase) in acetaminophen-treated rats. According to Tharun and Pavan Kumar (2013), aqueous extracts of *P. tirupatiensis* had the highest DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenging activity, accompanied by nitric oxide, hydrogen peroxide, and reducing ability. Kumar (2016) found that administering an aqueous extract of *P. tirupatiensis* to diabetic rats prevented a decrease in tissue GSH and ascorbic acid concentrations by scavenging free radicals and thereby reducing the consumption

of GSH and ascorbic acid. The occurrence of antioxidant compounds in *P. tirupatiensis* could account for this. The antioxidant behavior of the extracts showed that they had a concentration-dependent scavenging effect on superoxide anion radicals and hydroxyl radicals. The plant is said to have broad-spectrum antimicrobial and antioxidant activity.

7.3.3 Nephroprotective Activity

Palani et al. (2009a) reported that ethanol extract of *P. tirupatiensis* in two dose levels of 500 mg/kg and 750 mg/kg B/W, respectively on Acetaminophen (APAP) induced toxicity in rats were significantly decreased blood hematological parameters such as hemoglobin, packed cell volume, and mean corpuscular volume (MCV) values together with a significant increase in mean corpuscular hemoglobin concentration, neutrophils, and platelet concentration, together with an increase in body weight and reduction in uric acid (UA).

7.3.4 Hepatoprotectivity Activity

Palani et al. (2009b) found that oral administration of an ethanol extract of *P. tirupatiensis* at doses of 250 mg/kg and 500 mg/kg B/W reduced the levels of glutamate oxaloacetate transaminases (GOT), glutamate pyruvate transaminases (GPT), and alkaline phosphatase (ALP) thus increasing total protein content, preventing acetaminophen.

7.3.5 Anti-Diabetic Activity

Rajeswara Reddy et al. (2012) tested the therapeutic potential of an ethyl alcohol extract of *P. tirupatiensis* tuberous roots by measuring the activities of selective mitochondrial enzymes in diabetic rats caused by streptozotocin (STZ). The activities of oxidative enzymes malate dehydrogenase (MDH), glutamate dehydrogenase (GDH), succinate dehydrogenase (SDH) and isocitrate dehydrogenase (IDH) were significantly reduced in diabetic rats (ICDH). Diabetic rats had slightly higher lactate dehydrogenase (LDH) activity. The above improvements were significantly reversed in diabetic rats after 30 days of daily oral care with *P. tirupatiensis* ethyl alcohol extract (750 mg/kg body weight/day). *P. tirupatiensis* ethyl alcohol extract changed the

activities of oxidative enzymes, implying that it plays a part in mitochondrial energy production. The findings were compared to Glibenclamide, a popular anti-diabetic medication.

Rajeswara Reddy et al. (2013) treated STZ-induced diabetic rats for 30 days with *P. tirupatiensis* aqueous extract (750 mg/kg). When STZ-induced, diabetic rats were compared to normal, the contents of UA, xanthine oxidase activity (XOD), and malondialdehyde (MDA) were significantly increased by 50%, while the contents of GSH, and Ascorbic Acid (AA) were significantly decreased by 45% and 42%, respectively. The quality of UA, GSH, AA, MDA, and XOD activity were all stabilized after treatment with aqueous extract and glibenclamide. Control rats given an aqueous extract of *P. tirupatiensis* showed no noticeable improvements.

Narasimhulu et al. (2014) gave the EtOAc extract of *P. tirupatiensis* leaves to STZ (55 mg/kg body weight)-induced diabetic rats for 4 weeks and observed that the diabetic rats lost less weight and consumed less food and water, which was due to improved glycemic control and lower activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In STZ-induced diabetic rats, *P. tirupatiensis* extract can protect against diabetic complications, which may be due to the activation of cells to secrete insulin.

In diabetic animals, Kumar (2016) found that oral administration of *P. tirupatiensis* extracts and glibenclamide reduced MDA, UA content, XOD activity, and increased GST, ascorbic acid, and GSH activity in brain homogenates. The aqueous extract of *P. tirupatiensis* has a therapeutic protective role in diabetes patients by reducing oxidative stress and brain damage.

According to Venkatasubbaiah et al. (2017), *P. tirupatinensis* has antioxidant and anti-hyperglycemic properties that help to prevent the development of diabetes and its complications. They also demonstrated that *P. tirupatinensis* has good glycemic regulation in diabetes mellitus (DM) in pre-clinical and preliminary studies. These activities are linked to the inhibition of key enzymes that regulate carbohydrate metabolism, as well as increased insulin release and insulin sensitivity. Pt has a calming effect against diabetic complications, which is another significant feature of its advantages.

7.3.6 Cardioprotective Activity

Vijay et al. (2011) investigated the effects of an ethanolic extract of *P. tirupatiensis* given orally for 14 days at two doses (250 mg and 500 mg/kg body weight) on DOX-induced cardiotoxicity. When DOX-treated animals were compared to normal animals, significant cardiotoxicity, depletion

of endogenous antioxidants, and biochemical parameters were observed. Pre-treatment of DOX-induced rats with BA significantly reduced altered biochemical variations such as marker enzymes (SGPT, SGOT, CPK, ALP, and LDH), lipid profile, very low-density lipoprotein (LDL), triglycerides, high density lipoprotein (HDL), and total cholesterol), as well as antioxidant parameters SOD, GSH, CAT, GSH peroxidase, malondialde on pretreatment with *P. tirupatiensis*, serum urea and UA, which increased after DOX administration, returned to near-normal levels. The Dox-induced heart of rats pretreated with *P. tirupatiensis* had a significant recovery from cell injury, according to histology.

KEYWORDS

- *Pimpinella tirupatiensis*
- antioxidant activity
- cardioprotective activity
- antidiabetic activity
- isocitrate dehydrogenase
- malate dehydrogenase
- mean corpuscular volume

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CHAPTER 8

Anthology of Chemical Diversity of Bioactive Molecules and Therapeutics of the Genus *Swertia chirayita* (Roxb. ex Flem.) Karsten (Syn. *Gentiana chirayita* Roxb. ex Flem.)

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8.1 INTRODUCTION

Swertia chirayita, belonging to the family Gentianaceae is an endangered species. It is an erect, annual or biennial, branched herb, reaches up to 1.5 m in height. Cylindrical stem in basal region, robust, and quadrangular with increasing branches. Leaves are sessile, opposite, lanceolate or ovate with acuminate apex and rounded base, with entire margin with 3–7 prominent veins. Inflorescence consisted of large leafy panicles of solitary-axillary cluster of 3–5 flowers. Flowers are perigynous, yellow-green externally while appear purple internally, tetramerous (with four-lobed calyx and corolla), four stamens, unilocular ovary with parietal placentation. Fruit is an ovoid yellowish-brown, ellipsoid with many minute, globose capsule with bitter taste. It is indigenous and scattered throughout the temperate Himalayas, between 1200 m and 3000 m altitudes, extending from Kashmir, Himachal Pradesh, Uttarakhand, Arunachal Pradesh, Meghalaya, and Sikkim between altitudinal ranges up to China, Tibet, and Bhutan. Customary folklore

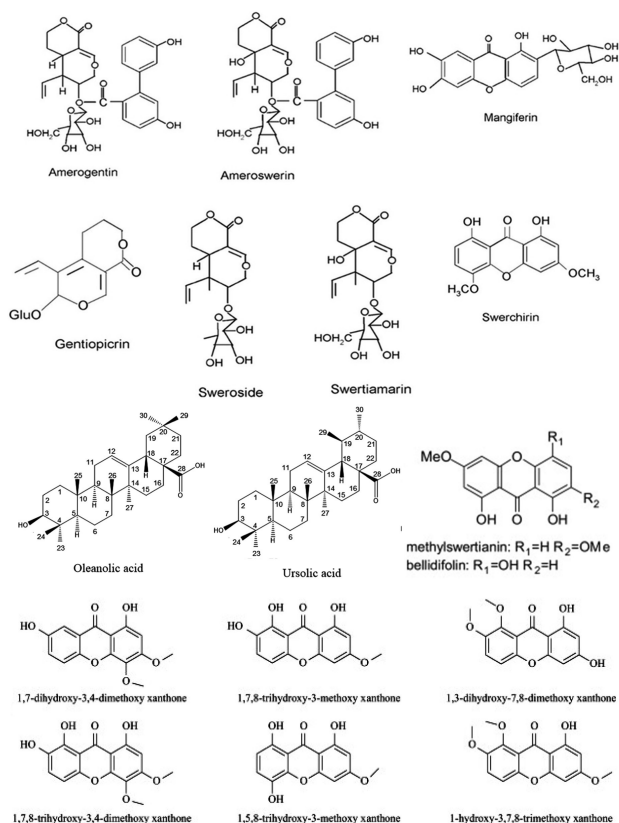
medicine included different substitutes of *S. chirayita* like *S. decussata*, *S. japonica*, *S. angustifolia*, *S. hookeri*, *S. petiolata*, *S. calycina*, *S. corymbosa*, *S. macrosperma*, *S. paniculata*, *S. punctata*, *S. purpurascens*, *S. chirayita*, *S. franchetiana*, *S. bimaculata*, *S. densifolia*, and *S. lawii*, being used in India, China, Pakistan, Japan, and other Asian countries. Vernacular names of the plant include Chirata (Hindi), Kirata-tikta (Sanskrit), Charaita/Charatin (Punjabi), Kiraita (Marathi), Nilabevu (Kannada), Nilavaembu (Tamil), Nain-ihabandi (Farsi) and Kasbuzarira (Arabic). It can be cultivated in Himalayan parts via seeds into proper seedbed followed by seedlings which transplanted into fields. Being commercial utility of whole plant, extra care is maintained since uprooting to stem drying till leaves detachment. Entire plants impart significance in folk, Unani, Ayurveda, Homeopathy, and allopathy. This is traded at local, regional, national, and internationally. Huge raw drug stores are located in Tanakpur, Ramnagar, Kolkata, Siliguri, and Delhi while limited raw drug is yielded from Kumaon (UK) and Sikkim markets @ of 75/-Kg (Selvam, 2012).

8.2 BIOACTIVES

Diversity of bioactive compounds were present in *S. chirayita* like amarogentin (bittermost), xanthenes, iridoids (glycoside) and their derivatives, alkaloids, lignans, terpenoids, flavonoids (mangiferine), secoiridoids, and along with other compounds such as chiratin ($C_{26}H_{48}O_{15}$), ophelic acid ($C_{13}H_{20}O_{10}$), palmitic acid, oleic acid, and stearic acid (Patil et al., 2013) while potassium, magnesium, and calcium (carbonate and phosphate), were obtained from its ash. But pharmacological activity of *S. chirayita* is associated with the phytoconstituents like amarogentin, swertiamarin, mangiferin, swerchirin, sweroside, amaroswer, and gentiopicroin. Ghosal et al. (1973) described about nine different kinds of tetraoxygenated xanthenes obtained from the herb as: 1, 5, 8-trihydroxy-3-methoxyxanthone (I), 1-hydroxy-3, 5, 8-trimethoxyxanthone (II), 1-hydroxy-3, 7, 8-trimethoxyxanthone (III), 1, 8-dihydroxy-3, 5-dimethoxyxanthone (IV), 1, 8-dihydroxy-3, 7-dimethoxyxanthone (V), 1, 3, 6, 7-tetrahydroxyxanthone-C2-D-glucoside (mangiferin, VI), 1, 3, 8-trihydroxy-5-methoxyxanthone (VII), 1, 3, 5, 8-tetrahydroxyxanthone (VIII) and 1, 3, 7, 8-tetrahydroxyxanthone (IX) respectively, while all such xanthenes of *S. chirayita* associated with medicinal importance. Xanthenes are bioactive substances which have the potential to serve as an anti-inflammatory, CNS depressant, antimalarial, antiulcerogenic, spasmogenic agent and blood sugar lowering agent (Kumar and Van Staden, 2016). Singh et al. (2012)

isolated) a new xanthone; 1, 5-dihydroxy-3, 8-dimethoxyxanthone (chiritol) from the herb. In addition to the tetraoxygenated xanthenes (I-IX), various monoterpene, triterpenes alkaloids and heterosides, were isolated from this herb. Oleanolic acid, ursolic acid, bellidifolin, syringaresinol, and β -amyrin derived from the *S. chirayita* plant associated with antimicrobial, antitumor, hypoglycemic, hepatoprotective, and anti-inflammatory action, respectively (Aleem and Kabir, 2018). While the alkaloids gentianine, gentiocrucine, enicoflavine, swertinin, swertianin, decussatin, isobellidifoli swertiamarin, friedelin, sitosterol, threonine, leucine, arginine, tryptophan, methionine, glutamic acid, and aspartic acid were obtained from aerial part and root of *S. chirayita*. Keil et al. (2000) and Wang et al. (2009) isolated amarogentin and 1,3,5,8-tetrahydroxyxanthone from *S. chirayita*'s root culture while its callus, multiple shoots, mother plant and regenerated plant culture produced amarogentin and amaroswerin (Koul et al., 2009).

Structures of important phytoconstituents of *S. chirayita* are given below:



8.3 PHARMACOLOGY

The plant has diverse clinical significance as discussed in subsections.

8.3.1 Hepatoprotective Activity

Traditional Ayurvedic medicine commercially utilizes *S. chirayita* extracts in the liver diseases or hepatoprotectants (Balasundari et al., 2005; Luo et al., 2009) under *in vivo* conditions. Phytochemicals like Swerchirin (Ya et al., 1999), Sweroside (Liu et al., 1994), Syringaresinol (Chakravarty et al., 1994) obtained from *S. chirayita* exhibit hepatoprotective properties. Methanolic extract of the whole plant treated dose @ 100 mg/kg body weight of animal were exhibit overall defense up to 81% and 78% as compared to galactosamine and paracetamol (PCM) (Karan et al., 1999; Nagalekshmi et al., 2011). They observed that plant extract is rich in secoiridoids against these two hepatotoxins, suggests its comprehensive attribute in the liver via inducing hepatotoxicity. Amarogentin (glycoside) presence in *S. chirayita* significantly protects the liver against carbon tetrachloride toxicity at (@ different doses, viz, 20, 50 and 100 mg/kg body wt. daily) in albino rats (Mukherjee et al., 1997; Khanal et al., 2014).

8.3.2 Hypoglycemic Effect

Recently Dey et al. (2019) treated DM (diabetes mellitus) induced experimental rats with ethanolic extract of *S. chirayita* and found significant control in diabetes. Methanolic extract of *S. chirayita* contains a large concentration of natural flavonoids, xanthones, and secoiridoids which prevents hyperglycemic condition and served antidiabetic (Alam et al., 2009; Alam et al., 2011; Sekar et al., 1987; Kumar and Van Staden, 2016) function. Swerchirin (1,8-dihydroxy-3, 5-dimethoxyxanthone) is a potent compound exerted lowering of blood sugar level in tolbutamide pretreated and glucose loaded, fed, fasted experimental model albino rats (Hirakawa et al., 2005). Suryawanshi et al. (2009) isolated Swerchirin from crude extract of *S. chirayita* and its effective in blood sugar lowering up to 60% at the dosage of 50 mg/kg, b.w. orally within seven hours of the treatment. Kohli et al. (2004) observed that hypoglycemic potential in Diabecon is associated with *S. chirayita* antioxidant property. Research findings stated that Swerchirin has equivalent anti-hypoglycemic effect as tolbutamide, centipiperalon,

and glibenclamide (Singh et al., 2012; Verma et al., 2013) drugs. Ethanolic extract of *S. chirayita* whole plant potentially reduced the blood sugar level in fasted, glucose fed and tolbutamide pretreated animals when the animals were injected with 250 mg/kg plant extract (Kar et al., 2003). Hexane fraction (250 mg/kg, b.w. orally for 28 days) of *S. chirayita* plant, tested in albino rats increased glycogen amount in liver and induces secretion of insulin from pancreatic β -cells by lowering of blood sugar (Chandrasekhar et al., 1990). Various valuable therapeutic phytoconstituents like swerchirin (Bajpai et al., 1991), bellidifolin, and isobellidifolin (Basnet et al., 1995), amarogentin (Phoboo et al., 2013), mangiferin (Muruganandan et al., 2005), swertiamarin (Vaidya et al., 2013) and swertinin derived from the extract of *S. chirayita* utilized in the treatment of diabetes (Dey et al., 2019).

8.3.3 Antioxidant Activity

The methanolic extracts from the aerial part of *S. chirayita* show antioxidant activity via xanthenes, phenolics, flavonoids, and secoiridoids which scavenges toxic free radicals (superoxide, hydroxyl radicals, and singlet oxygen species) or oxidative substrates and mediated lipo-peroxidation induction (Chen et al., 2011; Mahmood et al., 2014; Sanchez et al., 2000; Sankar et al., 2017). Balasundari et al. (2005) concluded that xanthenes content of *S. chirayita* enhanced lipid peroxidation products formation with reduced lethal cell injury against CCl_4 via antioxidant enzyme activities. *In vitro* testing of methanolic, ethanolic, aqueous extract of whole *S. chirayita*, plant against butylated hydroxyl anisole and Gallic acid, respectively favors their antioxidant potential (Ahirwal et al., 2014; Kshirsagar et al., 2015). The reaction of the extracts of *S. chirayita* with dimethyl p-phenylenediamine dihydrochloride (DMPD) yielded an important solid synthetic radical which showed fast radical scavenging ability and inhibition up to 30% (Singh et al., 2012).

8.3.4 Anti-Inflammatory Effects

Different extracts of *S. chirayita* plant in (whole plant in crude benzene extract, petroleum extract of aerial parts and ethanolic extract of roots, respectively) exhibit anti-inflammatory activity (Khanal et al., 2014; Banerjee et al., 2000; Kumar et al., 2003; Das et al., 2012; Alam et al., 2009) against Diclofenac treated mice @ 10–25 mg/kg due to presence of the xanthone derivatives (1, 5-dihydroxy-3, 8-dimethoxy xanthone). Various bioactive

compounds like Chiritol, β -Amyrin, Oleanolic acid derived from *S. chirayita* plant exhibit anti-inflammatory properties (Banerjee et al., 2000; Holanda et al., 2008; Naglekshmi et al., 2011) respectively. An aqueous suspension of *S. chirayita*, aerial parts in combination of 5% gum acacia significantly reduced the inflammation or hind paw-edema in albino rat models @ 50 mg/kg body weight (oral route) against Dextran, Bradykinin, and Carrageenin (Singh et al., 2012). Still, other drugs like phenylbutazone (50 mg/ kg) and betamethasone (0.5 mg/kg) were found to be more effective over *S. chirayita* during acute and subacute inflammation in experimental model study. Saravanan et al. (2014) reported that swertiamarin reduced the arthritis inflammation via regulation of transcription factors NF-kB/IkB and JAK2/STAT3 significantly. Dey et al. (2019) reported that *S. chirayita* is used in the treatment of choleric, inflammatory, and hepatic diseases while important phytochemical sweroside is used to treat osteoporosis (Sun et al., 2013).

8.3.5 Antimalarial Activity

Methanolic/Ethanolic/Petroleum extract from leaves/stem of *S. chirayita* was significantly effective against *Plasmodium falciparum*/malarial disease (Bhat and Surolia, 2001) which parasitized the red blood cells. Xanthone (1-Hydroxy-3,5,8-trimethoxyxanthone) and gentianine existence make it anti-malarial plant (Mandal and Chatterjee, 1994; Natarajan et al., 1974; Banerjee et al., 2000). Bhat and Surolia (2001) treated malaria strain *Plasmodium falciparum* FCK 2 with organic solvent and aqueous extracts obtained from *S. chirayita* under *in vitro* conditions. Assessment of antimalarial activity of the plant extracts was monitored with thin blood smears formation and their quantification with insertion of [35S]-methionine to parasite (*P. falciparum*) proteins determine value of (IC_{50}) that inhibits it. Ethanolic extract of whole plant was found to be effective against *Aedes aegypti* due to its larvicidal properties (Balaraju et al., 2009).

8.3.6 Gastroprotective Activity

Rafatullah et al. (1993) observed that the ethanolic extract of *S. chirayita* remarkably decreased the effect of indomethacin and necrotizing substances which caused gastric mucosal damage. Different phytochemicals derived from *S. chirayita* like amarogentin, amaroswerin (Niiho et al., 2006), 1-Hydroxy-3,7,8-Trimethoxyxanthone (Ateufack et al., 2007, 2014) utilized

as gastroprotective, antiulcerogenic, and spasmogenic agent. Pretreated rats with ethanolic extract of *S. chirayita* reinstated non-protein sulphhydryl content in the glandular stomachs with reduction in mucus depletion around gastric wall. Bhatt and Surolia (2001) reported that ethanolic extracts of *S. chirayita* alone and in combination with other plants also possess anti-ulcerogenic properties. Remarkable reduction in acidic gastric secretions volume and ulcer index was associated with the administration of the *S. chirayita* extract by Patil et al. (2013).

8.3.7 Anticarcinogenic Activity

Potential anti-carcinogenic activity observed in Amarogentin (Pal et al., 2012), Ursolic acid (Jesus et al., 2015), Swertiamarin (Kavimani and Manisenthikumar, 2000), Oleanolic acid (Kumar et al., 2017) and xanthenes isolated from *S. chirayita* (Banerjee et al., 2000; Sankar et al., 2017). Hexane extract from the whole plant of *S. chirayita* have significant concentration of ‘Amarogentin’ which activates different detoxification enzymes like glutathione S-transferases (GST), glutathione-peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) in different level after treatment (Saha et al., 2006). Chemical carcinogenic compound malondialdehyde (MDA) formation is not only reduced during lipid peroxidation via activation of detoxifying enzymes but also multiplicity of papillomas incidence get also inhibited. Chemoprotective compound amarogentin fraction potentially induced antiproliferative and apoptotic activity in carcinogenesis experimental mouse model (Soica et al., 2014). Yoshimi et al., 2001 investigated mangiferin (natural glucosylxanthone occurred inside *S. chirayita*) regulate bowel carcinogenesis in male F344 rats. Subedi and Karki (2018) evaluated anticancer properties of crude extract of *S. chirayita* against human cancer cell line like MCF-7, KELLY, and CACO-2 causing (breast cancer, brain, and colon cancer) respectively.

8.3.8 Antileishmanial Activity

S. chirayita, yielded glycoside ‘Amarogentin,’ showed strong antileishmanial activity which was tested as alone and two forms like liposomes and niosomes vesicles. Findings of Medda et al. (1999) and Sankar et al. (2017) suggested that vesicular bound amarogentin was found superior leishmanicidal agent rather free/alone amarogentin. Thus, amarogentin inserted liposomes or niosomes may serve as a significant tool in the treatment of leishmaniasis.

Ray et al. (1996) concluded that methanolic extract of *S. chirayita* is enriched with secoiridoid glycoside used to inhibit topoisomerase I enzyme of *Leishmania donovani* which prevent the leishmaniasis disease.

8.3.9 Antihelmintic Activity

Bachani (2019) reported that *in vitro* crude aqueous and methanolic extracts @ 25 mg/ml of whole plant of *S. chirayita* showed antihelmintic properties against live *Haemonchus contortus*. Besides, *in vivo* study, crude powder of the whole *S. chirayita* plant @ 3 g/kg (dose) given to naturally gastrointestinal nematodes infected sheep consequently reduced the number of eggs per gram of feces (Iqbal et al., 2006). Herbal extract of *S. chirayita* not only suppress the worms mobility but also reduced the egg number in sheep @3 g/kg up to 58.8 and 52.2%, respectively (Kshirsagar et al., 2019).

8.3.10 Antiviral Activity

Aqueous extract from leaves/stem of *S. chirayita* plant @ 1:64 dilution inhibited HSV-1 (Herpes simplex virus) induced plaque formation up to 70%. HSV-1 infected cells treated either with Acyclovir (antiviral drug) or *S. chirayita* extract regularly failed to exhibit amplification with PCR (Verma et al., 2008) which confirmed that plant extract is capable of DNA damage protection. Ethanolic extract of whole *S. chirayita* plant tested in HepG 2.2.15 cell line showed antiviral activity against Hepatitis B virus which is equivalent to antiviral drug Tenofovir (Zhou et al., 2015; Naglekshmi et al., 2011). Anti-HIV (human immune virus) activity reported by Kumar et al. (2016) and Guha et al. (1996) while various antiviral properties attributed by *S. chirayita* plant (Zheng and Lu, 1990; Kumar and Chandra, 2015; Sankar et al., 2017).

8.3.11 Anti-Central Nervous System (CNS) Depressant Activity

A glycoside swertiamarin (secoiridoid glycoside), gentianine, mangiferin, extracted from *S. chirayita* has significantly induced anti-central nervous system (CNS) depressant activity (Bhattacharya et al., 1974, 1976; Kavitha et al., 2013). Malhotra et al. (2007) observed that mangiferin-induced CNS-stimulating effects in experimental models like albino mice and rats were counter with swertiamarin activated anti-CNS depressant activity *in vivo* so

according to the condition swertiamarin and mangiferin is utilized. Ethanolic extract of whole *S. chirayita* possess xanthenes which is proven as CNS stimulant reported by Banerjee et al. (2000) and Sankar et al. (2017).

8.3.12 Fever Lowering Activity

Bhargava et al. (2009) reported that aqueous extract of root *S. chirayita* plant significantly control fever as PCM (150 mg/kg). Singh et al. (2012) reported that significant fever lowering was associated with 15 to 30 ml dose of herbal decoction prepared by boiling of 15 gm chirayata, cinnamon, and cloves in 250 ml of water. Sharma and Kumar (2017) orally administered methanolic extract of *S. chirayita* @ dose of 100 mg/kg and 200 mg/kg body weight of rats with the significant decrease in their body temperature against PCM.

8.3.13 Analgesic Activity

Alam et al. (2010) observed that ethanolic extract from leaf and stem of *S. chirayita*, and their different fractions, i.e., methanol, petroleum-ether, and dichloromethane fraction possess analgesic property in Swiss albino mice animal model where maximum inhibited by petroleum-ether fraction followed by methanol fraction. While ethanolic root extract of the same plant significantly served as analgesic activity (Das et al., 2012). Jauhri et al. (2018) stated that *S. chirayita* after successful exploration in many *in vivo/in vitro* research, human trials, clinical regard and it was found to be a promising candidate for modern medicine. A considerable large amount of analgesic and antipyretic compounds was obtained from the root of such plant (Dey et al., 2019).

8.3.14 Antimicrobial Activity

Aqueous and alcoholic extracts of *S. chirayita* has strong antimicrobial activity (Khan et al., 2018; Aleem and Kabir, 2018; Siler et al., 2010; Wang et al., 2001; Sankar et al., 2017; Kumar et al., 2017). Alam et al. (2009) reported that methanol/ethanolic/ dichloromethane and petroleum ether extract of *S. chirayita* possess remarkable antimicrobial properties towards some gram-positive and gram-negative bacteria while moderate activity against few fungi. Khan et al. (2018) reported that methanolic fraction of dried *S. chirayita* plant, R-14 possess strong antifungal activity against *Aspergillus*

niger. Laxmi et al. (2011) reported antifungal activity attributed by methanolic extract of whole plant treated test fungi like *Aspergillus niger* MTCC1881 and *Cladosporium oxysporum* MTCC against control Amphotericin (antifungal medicine). Sultana et al. (2007) screened bioactivity of *S. chirayita* fresh stem extracted in rectified spirit against 12 pathogenic bacteria and found their inhibition too. Yadav et al. (2016) concluded that *S. chirayita* plant can be easily explored as an antimicrobial agent against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecalis* at low concentration with minimum toxicity. Different *in vitro* antibacterial test evaluated with ethanolic extract of whole *S. chirayita* plant and methanolic extract of its stem administered into test organisms like *Pseudomonas aeruginosa* ATCC 25619/*E. coli* ATCC26922 and *Bacillus subtilis* ATCC 6633/*Pseudomonas aeruginosa* ATCC27853 against control antibiotic Ciprofloxacin, respectively (Rehman et al., 2011; Khalid et al., 2011).

8.3.15 Antiurolithiatic Activity

Parmar et al. (2012) evaluated the antiurolithiatic activity of *S. chirayita* stems in rats. The ethylene glycol feeding resulted in an increased level of promoters with a decreased level of inhibitors as compared to normal control rats. All these conditions were significantly reversed with treatment of *S. chirayita*. Histopathological analysis also revealed deposition of calcium oxalate (CaOx) crystals and disruption of tubular cells and juxtaglomerular cells. That deposition and disruption were also reduced in rats treated with *S. chirayita*.

KEYWORDS

- catalase
- central nervous system
- dimethyl p-phenylenediamine dihydrochloride
- glutathione S-transferases
- glutathione-peroxidase
- *Swertia chirayita*
- *Gentiana chirayita*

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CHAPTER 9

Biomolecules and Pharmacology of *Tabernaemontana divaricata* (L.) R.Br. ex Roem. & Schult.

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9.1 INTRODUCTION

Plants are a rich source of different kinds of bioactive molecules. The presence of these compounds may be the reason behind the pharmacological potential of plants. A deep understanding of bioactive principles in plants are valuable, as these compounds can be used by mankind for various purposes such as pharmaceuticals and other industries (Raju and Rao, 2020; Wankhede et al., 2013). Plant extracts have been used by more than half of the world population for the treatment of various diseases. The use of plants as medicine has attained a valuable position in health system all over the world (Hari et al., 2012).

Tabernaemontana divaricata (L.) R.Br. ex Roem. & Schult. is commonly known as crape jasmine and belongs to the family Apocynaceae. It is a small shrub with milky latex. Leaves are opposite, lanceolate, acuminate, with dark green color. Flowers are snow-white, solitary or few-flowered cymes which are axillary or terminal. It is a common garden plant, it has high medicinal value. It has been used in the traditional systems of medicine all over the world. The medicinal properties of its leaves and flowers are well known. It is one of the important genera that is used in Chinese, Ayurvedic, and Thai traditional medicine (Bijeshmon and George, 2014; Jain et al., 2010b; Raj and Balasubramaniam, 2011). The present review focuses on the studies on pharmacological properties of *T. divaricata* and aims to summarize the pharmaceutical potential of the plant.

9.2 BIOACTIVE COMPOUNDS

In an attempt to find the phytochemical composition of ethanolic extract of whole plant of *T. divaricate* Poornima and team has detected the presence of alkaloids, flavonoids, glycosides, polyphenols, steroids, and tannins, confirmed by the HPTLC analysis (Poornima et al., 2017). In another study, phytochemical screening of aerial parts of *T. divaricata* indicated the presence of alkaloids, proteins, and phytosterol (Rathaur et al., 2020).

Qualitative identification of phytochemical constituents in ethanolic and aqueous extracts of leaves of *T. divaricata* revealed the presence of alkaloids, tannins, resins, proteins, amino acids, flavonoids, saponins, phenols, glycosides, steroids, tri-terpenoids, fixed oils, and fats (Raj and Balasubramaniam, 2011). Preliminary screening of phytochemicals was done in petroleum ether, aqueous, and ethanolic extract of leaves of *T. divaricata*. It was found that the petroleum ether extract showed the presence of steroids, fat, and fixed oils; the aqueous extract gave positive result for carbohydrates, amino acids, steroids, flavonoids, alkaloids, glycosides, and tannins; and the ethanolic extract contained same phytochemical constitution of that of aqueous extract (Jain et al., 2010b). The preliminary phytochemical screening was carried for leaf extracts of the plant and results indicated the presence of carbohydrates, alkaloids, glycosides, terpenoids, phenols, tannins, flavonoids, steroids, proteins, and amino acids (Radhika, 2018). In another study, phytoconstituents present in an ethanolic extract of the leaves of *T. divaricata* was evaluated through GC-MS analysis and found the presence of 96 phytochemicals, of which 17 are reported to be bioactive (Anbukkarasi et al., 2016).

Hari et al. (2012) identified the presence of sterols, carbohydrates, flavonoids, proteins, alkaloids, and tannins from the hydroalcoholic flower extract of *T. divaricata* by thin-layer chromatography and qualitative phytochemical analysis. Two new indole alkaloids were isolated from the twigs and leaves of *T. divaricata*. They are (3R)-7,19-di-epi-3-methoxytabernoxidine (1) and (3R,19R)-19-hydroxy-3-(2-oxopropyl) voacangine (2). Their structures are presented in Figure 9.1 (Li et al., 2019).

An alkaloid, pseudovoboparicine 1 was isolated by means of prep TLC from the rootbark of *T. divaricata* (van Beek et al., 1985). In a study, two new monoterpenoid indole alkaloids, Tabervarines A and B were isolated from the methanol extract of the twigs and leaves of *T. divaricata*. The structure of the compound Tabervarines A (1) and B (2) depicted in Figure 9.2 (Yuwen et al., 2019). The quantification of conophylline was done from the leaves of *T. divaricata*. Pancreatic lipase inhibitory activity of the alkaloid rich

fractions showed a correlation to their, respective conophylline content. The structure of the compound is depicted in Figure 9.2 (Sridhar et al., 2018). A bisindole alkaloid 3-R/S-hydroxyvoacamine was isolated from stem extract of *T. divaricata*, which possesses acetylcholinesterase (AChE) inhibiting activity. The structure of the compound is depleted in Figure 9.2 (Chaiyana et al., 2013).

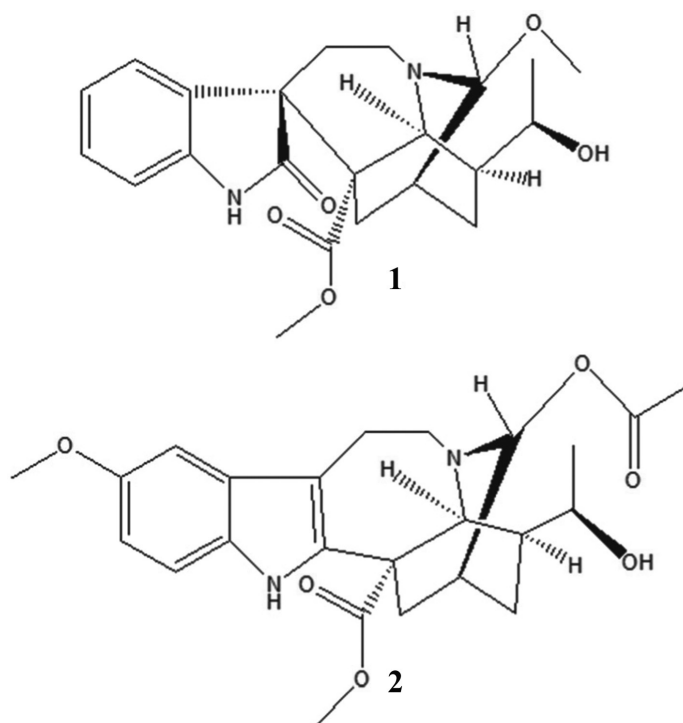


FIGURE 9.1 Structure of (3R)-7,19-di-epi-3-methoxytabernoxidine (1); and (3R,19R)-19-hydroxy-3-(2-oxopropyl) voacangine (2).

Source: Redrawn from: Li et al. (2019).

Four different alkaloids were isolated from the methanolic extract of *T. divaricata* aerial parts by activity-guided fractionation for Wnt signal inhibitory activity, they are voacangine (1), isovoacangine (2), coronaridine (3), and coronaridine hydroxyindolenine (4) and their structure is given as Figure 9.3. These compounds exhibited TCF/b-catenin inhibitory activity. Coronaridine inhibit the Wnt signaling pathway by decreasing the mRNA expression of β -catenin (Ohishi et al., 2015).

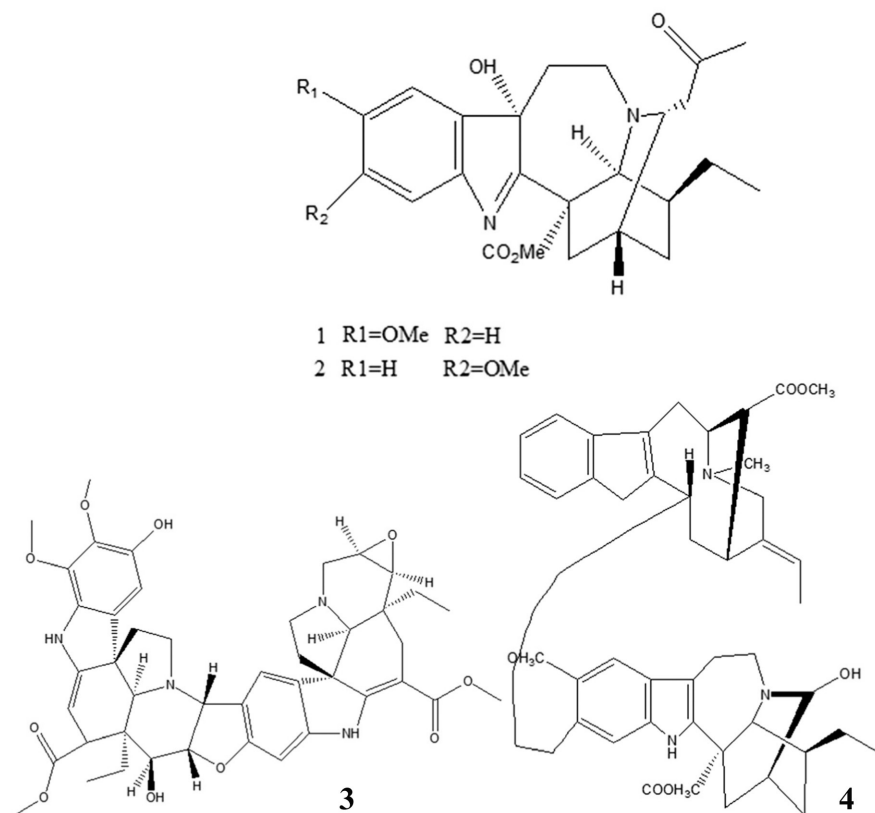


FIGURE 9.2 (1) structure of Tabervarin A; (2) structure of Tabervarin B; (3) R/S-hydroxyvoacamine and conophylline (4).

Source: Redrawn from: Chaiyana et al. (2013); Sridhar et al. (2018); Yuwen et al. (2019).

9.3 PHARMACOLOGY

9.3.1 Antibacterial Activity

Methanolic extracts of *T. divaricata* stem bark was analyzed for antimicrobial efficacy by agar well diffusion method and the plant showed potential antibacterial activity against *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus* (Baishya et al., 2018). The latex of *T. divaricata* was analyzed for the antibacterial activity by well diffusion method. It possesses significant antibacterial activity against *Enterococcus faecalis* (Raju and Rao, 2019).

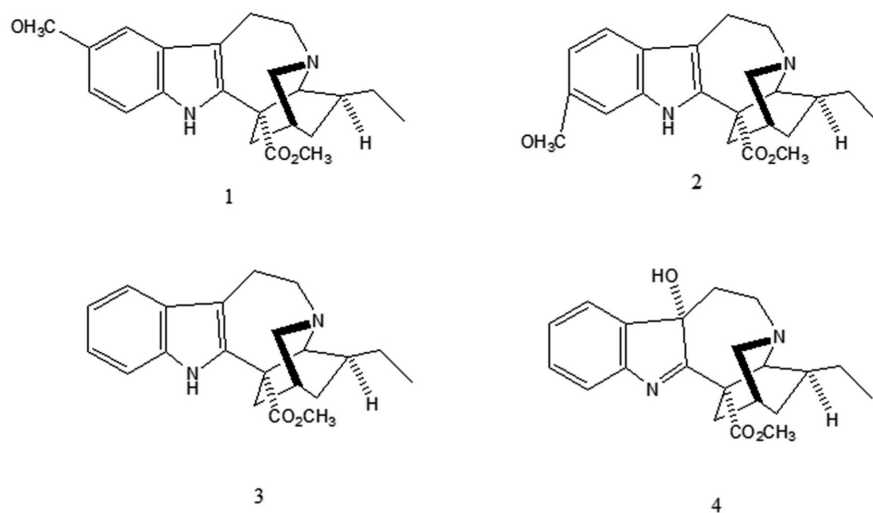


FIGURE 9.3 Structure of alkaloids isolated from *T. divaricata* aerial parts: Voacangine (1); isovoacangine (2); coronaridine (3); and coronaridine hydroxyindolenine (4).

Source: Redrawn from: Ohishi et al. (2015).

The methanolic flower extract of *T. divaricata* possesses potent antibacterial properties against *Staphylococcus aureus* and *Escherichia coli* (Bijeshmon and George, 2014). Extract of *T. divaricata* flowers were analyzed for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Proteus vulgaris*. Antibacterial activity was investigated by agar cup plate method. It is revealed that the extract possesses significant antibacterial activity in a dose-dependent manner (Sahoo et al., 2016).

In another study agar well diffusion was done to evaluate antimicrobial activity of various leaf extracts of *T. divaricata* against different bacteria. The extracts showed moderate inhibitory effect against both species of bacteria (Raj and Balasubramaniam, 2011). Antimicrobial activity of various leaf extracts of *T. divaricata* were analyzed and found significant activities (Ashikur et al., 2011). Chloroform and methanol extracts of leaves of *T. divaricata* were evaluated for their antibacterial activity against 4 pathogens bacteria. Methanol soxhlation extract showed remarkable antibacterial activity against most tested bacteria (Radhika, 2018).

Zinc oxide nanoparticles were synthesized using aqueous *T. divaricata* green leaf extract and the nanoparticles showed higher antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* and lesser antibacterial activity against *Salmonella paratyphi* compared to the standards (Raja et

al., 2018). Copper oxide nanoparticles were synthesized from *T. divaricata* leaves in another study, and antimicrobial activity of copper oxide nanoparticles were investigated and found inhibitory against common *Escherichia coli* (Sivaraj et al., 2014).

9.3.2 Antifungal Activity

Antifungal activity was tested using methanolic extracts of *T. divaricata* stem bark and the plant showed potential antifungal activity against *Candida albicans* (Baishya et al., 2018). The *T. divaricata* latex was analyzed for antifungal activity against *Aspergillus* species. The extract has no effect on *A. flavus*, but growth of *A. niger* was inhibited (Raju and Rao, 2019).

The different leaf extracts of *T. divaricata* were screened by Wankhede et al. (2013) for antifungal activity. The ethyl acetate (EtOAc) extract of leaf of *T. divaricata* showed MIC of 1 mg/ml against growth of *Candida albicans* ATCC90028 strain. Extract with distilled water, petroleum ether and methanol also inhibited the growth of *C. albicans*. Sequential distilled water extract of *T. divaricata* plant required a higher concentration to inhibit the growth of *C. albicans*.

9.3.3 Antioxidant Activity

A study proved that the oral administration of whole plant extract of *T. divaricata* to Fe-NTA intoxicated rats showed remarkable antioxidant property (Sundaram et al., 2015). The latex of *T. divaricata* was analyzed for antioxidant activity by DPPH assay and found moderate antioxidant activity (Raju and Rao, 2019). In the study, an induced neuronal loss produces memory impairment in mice. The mice pre-treated with *T. divaricata* root extract prevent the memory loss and decreased lipid peroxidation. The study assumes this might be mediated by its antioxidant property (Khongsombat et al., 2018).

The methanolic extract of the leaves of *T. divaricata* was evaluated for *in vitro* antioxidant potential and results revealed significant antioxidant activity in a dose-dependent manner (Rumzhum et al., 1970). Antioxidant potential of aqueous leaf extract of *T. divaricata* was screened using different *in vitro* assays. The study concluded that leaf extract of *T. divaricata* showed potent radical scavenging activity (Padmaja and Hemalatha, 2011).

Various assays were performed to evaluate the antioxidant activity of ethanolic leaf extract of *T. divaricata*. It was evident that the leaf showed

significant antioxidant activity in a dose-dependent manner (Kalaimagal and Umamaheswari, 2012). Petroleum ether, ethanol, and aqueous extracts of leaves of *T. divaricata* were analyzed for free radical scavenging activity and the ethanolic extract of *T. divaricata* showed 58.7 (0.62%) inhibition and aqueous extract showed 54.9 (0.53%) inhibition in the superoxide scavenging model. All extracts showed the concentration and time-dependent activity (Jain et al., 2010b). Ethanolic extract of the leaves of *T. divaricata* was analyzed, and the most potent antioxidant activity was measured at a maximum concentration of 10 mg/ml (Anbukkarasi et al., 2016).

9.3.4 Anticancer Activity

Selvakumar and Kumar (2015) investigated the inhibition of cell growth by aerial parts of *T. divaricata*. The results indicate the anticancer property of the plant against the human laryngeal carcinoma cell line. Cytotoxicity activity of crude petroleum ether and ethanolic leaf extracts of *T. divaricata* against different cell lines were analyzed by Doshi et al. (2017). The study was conducted on human colon cancer, human breast cancer and human leukemia cell lines. The extracts showed mild results on human breast cancer and human leukemia cell line and negative results on human colon cancer cell line. The methanolic leaf extract was evaluated for its cytotoxic effect using brine shrimp lethality bioassay, result indicated a potent cytotoxic effect (Rumzhum et al., 1970). In a study, cytotoxic analysis of ethanolic extracts of *T. divaricata* leaves were done, and the result found significant cytotoxic activity (Khan and Islam, 2012). In the study, hydroalcoholic extract of the flowers of *T. divaricata* have been tested for *in-vitro* anticancer activity. Analysis was performed against human cancer cell line and MTT assay. The results indicated that the extract possessed a moderate amount of anticancer activity (Dantu, 2012).

9.3.5 Antifertility Activity

Antifertility activity of ethanolic extracts of *T. divaricata* leaves on female rats were evaluated through estrogenic activity analysis. The result found that *T. divaricata* has remarkable antifertility activity (Jain et al., 2010a). The activity of *T. divaricata* leaf extract was tested orally on female albino mice, and the result suggests that the antifertility effect of *T. divaricata*, may be due to impairment in the release of luteinizing hormone (LH) and

follicle-stimulating hormone (FSH) (Jain et al., 2012c). Antifertility effect of *T. divaricata* leaf extract on male rats was also studied. The results found that 50% ethanol extract of *T. divaricata* leaf produced a change in spermatogenesis thus had an effect on reproduction (Jain et al., 2012b). A study was performed on female rats to evaluate the anti-implantation and anti-ovulatory effect of *T. divaricata* leaves. The result suggests that *T. divaricata* had an anti-implantation effect (Jain et al., 2012a). Mukhram et al. (2012) evaluated the antifertility effect of methanolic and aqueous flower extracts of *T. divaricata* in rats. The extract showed potent estrogenic, anti-implantation, and early abortifacient activities in a dose-dependent manner.

9.3.6 Antidiabetic Activity

Methanol extract of leaves of *T. divaricata* was analyzed for antidiabetic activity on alloxan induced diabetic male Swiss albino mice. The extract at a dose of 400 mg/kg lowered maximum blood glucose level at the 12th hour of the treatment period (Rahman et al., 2011).

9.3.7 Anthelmintic Activity

Anthelmintic activity of fresh and dried flower extract of *T. divaricata* was done using Indian earthworms. The extracts showed significant anthelmintic activity at different concentrations compared with that of the control Metronidazole, hence *T. divariacata* can be used against helminthiasis (Hari et al., 2012).

9.3.8 Analgesic Activity

Analgesic activity of methanol extract of aerial parts of *T. divaricata* was analyzed in healthy Wistar albino mice and rats. It was found that methanol extract of *T. divaricata* significantly inhibited the acetic-acid induced stretching in mice. Hot-plate and Tail-clip methods also showed strong analgesic effect. The study assumes that the analgesic activity of *T. divaricata* may be due to the presence of antioxidative constituents such as terpenoids and flavonoids in plant (Kanthlal et al., 2011). In analgesic test of *T. divaricata* leaves, writhing protection has shown at the doses of 250 and 500 mg/kg body weight in mice

at 22.02% and 33.93% respectively, i.e., the extract possesses significant activity (Khan and Islam, 2012).

9.3.9 Antipyretic Activity

Male Swiss albino rats were used for testing antipyretic activity against yeast induced hyperpyrexia using methanol extract of aerial parts of *T. divaricata*. At the doses of 100 and 200 mg/kg of extract found to decreased the rectal temperature in a dose dependent manner. Paracetamol (PCM) is used as standard (Kanthlal et al., 2011).

9.3.10 Anti-Inflammatory Activity

In vivo anti-inflammatory activity of *T. divaricata* leaf extract was evaluated on male albino mice through the ability to lower croton oil-induced edema. The methanolic leaf extract showed strong dose-dependent activity against edema in mice (Jain et al., 2013).

9.3.11 Antiulcer and Gastroprotective Activity

A study performed in methanolic extract of *T. divaricata* flowers for screening its antiulcer activity against aspirin and ethanol induced gastric ulcers in rats. It concluded that *T. divaricata* methanolic extract has shown significant gastroprotective effect by enhancing the production of the gastric mucosa or preventing its depletion (Khan et al., 2013).

Methanolic extract of *T. divaricata* flowers possesses acid neutralizing, anti-secretory, and ulcer preventive properties and thereby produces significant gastroprotective effect (Khan et al., 2011). The flowers of *T. divaricata* was tested *in vivo* in a study against gastric ulcerations that are experimentally induced by pylorus ligation. Ethanol extract produced inhibition on gastric ulcerations in a dose-dependent manner (Rasheed et al., 2013).

In the study on gastroprotective effects of extracts of *T. divaricata* leaves against ethanol, hydrochloric acid, aspirin, and indomethacin-induced gastric mucosal injury in rats. The ulcer index in the treated animals was found to be significantly less. The ethanolic extract at a higher dose was found to have a remarkable gastroprotective effect (Raj et al., 2014a).

9.3.12 Antidiarrheal Activity

T. divaricata methanolic extract of the leaves was analyzed for the antidiarrheal property. Diarrhea was induced by castor oil. The extract significantly decreases in several wet feces produced (Kumari et al., 2018). The hydroalcoholic and aqueous extracts of *T. divaricata* leaves were examined for antidiarrheal activity, against castor oil induced diarrhea and gastrointestinal motility in rats. The extract produced dose dependent action against induced diarrhea and also decreased gastrointestinal motility (Raj et al., 2013).

9.3.13 Hepatoprotective Activity

Ethanollic extract of whole plant of *T. divaricata* produced activity against Ferric nitrilotriacetic acid (Fe NTA) and diethylnitrosamine (DEN) induced hepatic necrosis. It was tested and evaluated in Fe NTA and DEN treated male Wistar albino rats. The study concluded the importance of use of *T. divaricata* in the treatment of hepatic necrosis (Poornima et al., 2014).

The hepatoprotective activity of hydroalcoholic extract of *T. divaricata* against PCM induced liver damage in rats was studied. The result found that the plant extract has significant effectiveness in protecting the liver against the injury. The study assumes that it may be due to reduction in serum enzymes alanine aminotransferase (ALT), bilirubin, etc. (Umarani and Chitra, 2012).

9.3.14 Acetylcholinesterase (AChE) Inhibitor Activity

In vivo AChE inhibitor activity was tested in rats using *T. divaricata* root extract. Different doses of *T. divaricata* root extract significantly inhibited AChE in a concentration-dependent manner (Chattipakorn et al., 2007). AChE inhibiting activity was analyzed from the stem extract of *T. divaricata* and the result showed that it depicted an IC_{50} value of $7.00 \pm 1.99 \mu\text{M}$ (Chaiyana et al., 2013). In another study, the effect of root extracts of *T. divaricata* on amyloid β_{25-35} peptides induced cognitive deficits and AChE activity in mice was tested. Amyloid β_{25-35} peptides induced memory impairment and increased levels of cortical and AChE activity. The treatment with ethanolic extract of *T. divaricata* significantly

improved the memory deficits by decreasing the levels of AChE activity (Nakdook et al., 2010).

9.3.15 Photocatalytic Activity

Zinc oxide nanoparticles were synthesized from aqueous *T. divaricata* green leaf extract and its photocatalytic activity was analyzed by the degradation of methylene blue dye with sunlight. UV-Visible spectrum of methylene blue has an absorption maximum at 660 nm. The dye solution with zinc oxide nanoparticles was irradiated with sunlight. The dye degradation was monitored by UV-Visible spectrum, and a gradual decrease in absorbance was observed with irradiation and dye gets completely degraded in 90 minutes, and this indicates the photocatalytic activity of zinc oxide nanoparticles (Raja et al., 2018).

9.3.16 Anticonvulsant Activity

T. divaricata ethanolic extract showed maximum anticonvulsant activity against maximal electroshock induced convulsion in adult male Swiss albino mice. The exact anticonvulsant mechanism of *T. divaricata* is not clear. It may be due to the presence of some phytochemicals that may be attributed to the anticonvulsant mechanism (Raj et al., 2014b). Anti-seizure potential of *T. divaricata* flower methanolic extract against maximal electroshock and pentylenetetrazole induced convulsions was studied. The extract was found to inhibit the occurrence of electrically and chemically induced seizures in rats and mice, respectively. The convulsions and percentage mortality were observed 50% less when compared to the control group in *T. divaricata* extract-treated animal models (Khan and Mukham, 2011).

9.3.17 Antinociceptive Activity

The ethanol extract of leaves of *T. divaricata* was screened for its preliminary antinociceptive activity and the extract shown remarkable writhing inhibition comparable to the standard drug diclofenac sodium (Sharker et al., 2011). The study evaluated the oral administration methanolic extract

of flower *T. divaricata* in antinociceptive effect and the result showed a significant antinociceptive effect in mice (Khan et al., 2018).

9.3.18 Anti-Cataleptic Activity

Anti-cataleptic activity of *T. divaricata* leaves was analyzed by Raj et al. (2014c). Aqueous and ethanolic extracts at 50, 100, and 150 mg/kg doses were studied against haloperidol-induced catalepsy in rats, and it is found that both aqueous and ethanolic extracts were found to reduce catalepsy significantly.

9.3.19 Anti-Cataractogenic Activity

Anticataractogenic activity of *T. divaricata* silver nanoparticles (AgNPs) biosynthesized using ethanolic extract of *T. divaricata* leaf were evaluated *in vivo* in rat pups. The result showed that the nanoparticles prevented selenite-induced cataractogenesis by maintaining near-normal lenticular activities of calcium, calcium transporter genes and proteins, total calpain, calpain isoform genes and proteins (Anbukkarasi et al., 2017).

9.3.20 Anticariogenic Activity

The anticariogenic potential of ethyl alcoholic extract of *T. divaricata* leaf extract was analyzed against *Streptococcus mutans* and *Lactobacillus acidophilus* using agar well diffusion method. The leaf extract was found bactericidal at higher dose and bacterio-static at lower dose (John and Cheriyan, 2020).

9.3.21 Catalase (CAT) and Protease Activity

In a study, latex of *T. divaricata* was analyzed for catalase (CAT) activity by the decomposition of H_2O_2 and was monitored by using a UV-Vis spectrophotometer. The result found that the latex of *T. divaricata* possessed mild CAT activity (Raju and Rao, 2019). A study was conducted in latex of *T. divaricata* for protease activity, which was determined by the hydrolysis of milk casein proteins. The result found high protease activity in plant latex (Raju and Rao, 2019). Some proteases were isolated from the latex of *T.*

divaricata and protein yield was 30 mg/ml. The proteases exhibit dose-dependent caseinolytic, fibrinogenolytic, and blood clot activities. So, the study supports the traditional use of plant latex to stop bleeding and wound healing (Banu et al., 2017).

The latex of initially *T. divaricata* was estimated for proteolytic activity using casein as the substrate. Crude enzymes from the plant exhibited coagulant activity and also a reduction in clotting time. It indicates the therapeutic application of latex of *T. divaricata* in wound healing process (Singh et al., 2015).

T. divaricata possess different pharmacologically active substances such as alkaloids, glycosides, saponins, tannins, flavonoids, and phenolic compounds, etc., which may be responsible for the pharmacological activities and therapeutic applications of the plant.

KEYWORDS

- **Apocynaceae**
- **Bioactive molecules**
- **Diethylnitrosamine**
- **Ferric nitrilotriacetic acid**
- **Pharmaceuticals**
- ***Tabernaemontana divaricata***

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CHAPTER 10

Phytochemistry and Pharmacology of *Sclerocarya birrea* (A. Rich.) Hochst.: A Review

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10.1 INTRODUCTION

Sclerocarya birrea, commonly known as ‘marula,’ belongs to the family Anacardiaceae. It is a deciduous tree that reaches up to 20 m in height. *S. birrea* is a highly used ethnomedicinal plant in Africa (Gouwakinnou et al., 2009). The fruits of *S. birrea* are edible and are used widely in African diet. The fermented fruits are given as a refreshing drink (Iwu, 1993). The fruits were reported to contain polyphenols, flavonoids, coumarins, tannins, phytosterols, and triterpenoids. The stem-bark, roots, and leaves of *S. birrea* also holds various medicinal values such as antidiabetic, antihypertensive, and anti-inflammatory activities (Gondwe et al., 2008). The bark alone or combined with other plants has been used to treat diarrhea, fever, boils, syphilis, hepatitis, rheumatism, and leprosy (Kokwaro, 1976).

10.2 BIOACTIVES

The barks of *S. birrea* contain 10–20% tannins and some alkaloids (Roodt, 1998). The *S. birrea* leaves contain tannins and flavonoids (Guèye, 1973). The leaves contain quercetin 3-*O*- α -L-rhamnopyranoside, Quercetin 3-*O*- α -L-(5''-galloyl)-arabinofuranoside, quercetin 3-*O*- β -D-(6''-galloyl) galactopyranoside, quercetin 3- β -D-glucopyranoside, kaempferol 3-*O*- β -D-(6''-galloyl)-glucopyranoside, kaempferol 3-*O*- α -L-rhamnopyranoside, myricetin 3-*O*- α -L-rhamnopyranoside, (-)-epigallocatechin 3-*O*-galloyl ester, (-)-epicatechin 3-*O*-galloyl ester, and gallic acid (Braca et al., 2003). The fruits of *S. birrea* have high nutritional values. The fruit juice is high in Vitamin C (2 mg/g) (Shackleton et al., 2002) and sesquiterpene hydrocarbons (Pretorius et al., 1985). The bioactive compounds in *S. birrea* are mentioned in Figure 10.1.

The wine from the fermented fruit is very famous that is high in alcohol content (15% per volume). The non-alcoholic fruit drink has also been in practice. The seed kernels are used in cooking as a substitute of other nuts. The seed kernel has 2699 to 2703 kJ/100 g of energy that is higher than other commonly eaten nuts. Both seed kernels and fruits are rich in minerals (iron, calcium, magnesium, and phosphorous) and proteins (Mojeremane and Tshwenyane, 2004). The seeds also contain oleic acid (67.2%), stearic acid (50.7%), linoleic acid (5.9%), palmitic acid (14.1%) and amino acids (Ojewole, 2004). The oil extracted from the nuts are low in Vitamin E but highly valued because of its low oxidizing properties (Shone, 1979). *S. birrea* has been a crucial source of nutrition in the times of drought and hunger.

10.3 PHARMACOLOGY

10.3.1 Antioxidant Activity

The methanolic extract of *S. birrea* root, leaves, bark, and seed kernel cake was reported to have antioxidant activity. The parts of *S. birrea* had shown varying antioxidant capacities as follows: Seed cake > root > leaves > bark. All the extracts had shown to inhibit linoleic acid oxidation and β -carotene bleaching when compared to the control. The DPPH (1,1-diphenyl-bpicrylhydrazyl) method also revealed the seed cake had the highest antioxidant capacity than other *S. birrea* parts (Mariod et al., 2008). The juice from *S. birrea* fruits were ascribed to high polyphenolic and flavonoid content, which also has high antioxidant and free radical scavenging activities that in turn involved in cell signaling pathways to regulate cell survival, growth,

and differentiation (Borochoy-Neori et al., 2008). *S. birrea* leaf extract was reported to have the highest flavonoid content, while *S. birrea* bark extract was reported to have the highest tannin content. Both flavonoid and tannin are natural antioxidants that play an important role in scavenging free radicals (Russo et al., 2018).

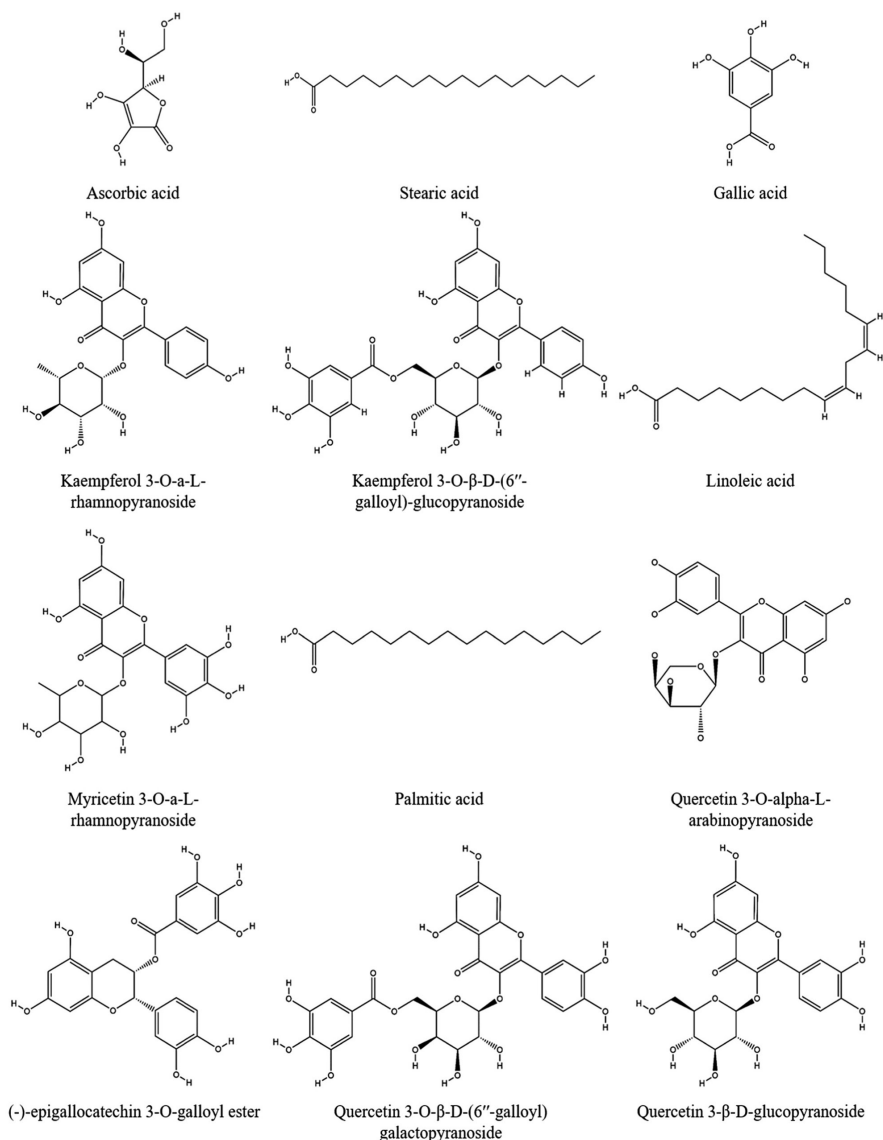


FIGURE 10.1 Bioactive compounds from *S. birrea* bark, fruit, and leaves.

10.3.2 Antimicrobial Activity

The antibacterial activity of bark and leaf extract of *S. birrea* showed inhibition against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* (Eloff, 2001). *P. shigelloides* and *S. pyogenes* were reported to be more susceptible than other bacteria (Gathirwa et al., 2008). The acetone extract of *S. birrea* exhibited inhibitory effect against *Helicobacter pylori* (Njume et al., 2011). Traditionally, *S. birrea* has been used for treating fungal infections in skin and oral candidiasis. Research on the methanolic root extract showed strong antifungal activity against *Candida albicans*, *C. tropicalis*, *C. krusei*, *C. parapsilosis*, and *Cryptococcus neoformans* (Masoko et al., 2008). The bark extract showed activity against *Candida parapsilosis*, *Rhodoturula mucilaginosa*, and *Cryptococcus albidus*. *S. birrea* is used for the traditional treatment for malaria. *S. birrea* was reported to have anti-plasmodial activity against *Plasmodium falciparum* and antimalarial activity against *Plasmodium berghei* (Gathirwa et al., 2008).

10.3.3 Antidiabetic Activity

S. birrea was extensively studied for its antidiabetic activity, hypoglycemic effect in normal and hypoglycemic animal models and cultured cells (Braca et al., 2003; Dièye et al., 2008; Dimo et al., 2007; Gondwe et al., 2008; Laurens et al., 1984; Ojewole, 2003). The stem bark extract was reported to show high hypoglycemic activity (Musabayane et al., 2006). The various parts of the plants were reported to show glucose utilization property in C2C12 muscle cell line and 3T3-L1 adipocytes (van de Venter et al., 2008). It also showed glucose homeostasis, reduced glucose and insulin levels in streptozotocin (STZ)-induced diabetic rat models (Dimo et al., 2007).

It exhibited cardioprotective effect on STZ-induced diabetic rats (Musabayane et al., 2006). The aqueous stem bark extract of *S. birrea* exhibited hypoglycemic effect and reduced glucose levels in a dose-dependent (100–800 mg/kg body weight) manner in STZ induced rats. The significant reduction in blood glucose levels is compared to the standard antidiabetic drug chlorpropamide. Along with modulating blood glucose levels, *S. birrea* also exhibited protection against kidney by modulating glomerular filtration rate (GFR) and arterial blood pressure (BP) in STZ-induced rats (Gondwe et

al., 2008). Overall, it showed improvement in insulin secretion, cardio, and reno-protective effects in diabetes mellitus (DM).

10.3.4 Anti-Inflammatory Activity

S. birrea has been used for inflammatory disorders in folk medicines. The research on *S. birrea* stem bark extract exhibited an anti-inflammatory effect on egg albumin induced edema in rat paw. It showed a time-dependent reduction in rat paw edema (Ojewole, 2003). The methanolic extract of *S. birrea* against carrageenan and histamine-induced rat paw edema exhibited maximum anti-inflammatory effect (Ojewole, 2004). Anti-inflammatory effect was achieved by histamine and prostaglandin pathway inhibition and its antioxidant effect (Fotio et al., 2009).

10.3.5 Anticancer Activity

The acetone extract of *S. birrea* bark exhibited anticancer activity against various cell lines (HT-29, MCF-7 and Hela) in time and dose-dependent manner. The treatment exhibited apoptosis induced cell death and antiproliferative effect (Tanih and Ndip, 2013). The methanolic root extract of *S. birrea* exhibited cytotoxicity against HepG2 (hepatocarcinoma cell line) in time and dose-dependent manner. The treatment induced apoptosis, reactive oxygen species (ROS), and reduced mitochondrial membrane potential to induce cancer cell death. Increased ROS occurs *via* inducing apoptosis that works through mitochondrial permeability transition complex. The treatment with methanolic root extract of *S. birrea* did not cause much effect on normal human dermal fibroblast, suggesting *S. birrea* causes cancer cell death but is less toxic to normal cells (Armentano et al., 2015).

10.3.6 Gastro-Intestinal and Hepatoprotective Activity

Traditionally in Africa *S. birrea* has been used for gastroenteritis, dysentery, and stomach-aches (Belemtougri et al., 2001). The lyophilized plant decoction exhibited antidiarrhoeic activity in magnesium sulfate and sodium picosulfate-induced diarrhea. The mechanism involved in antidiarrhoeic activity was related to intestinal transit inhibition. The condensed tannin, rich in procyanidin

from *S. birrea* exhibited inhibition of intestinal motility (Galvez et al., 1993). *S. birrea* showed antispasmodic effect in acetylcholine-induced spasm in rat duodenum, exhibited concentration-dependent reduction in the maximal response of acetylcholine (Belemtougri et al., 2006). Also (-)-epicatechin-3-galloyl ester isolated from *S. birrea* exhibited secretagogue activity (Peralta et al., 1992). *S. birrea* stem bark extract possess hepatoprotective activity in alcohol-carbon tetrachloride-induced liver damage in rats (Garba et al., 2006).

10.3.7 Antihypertensive Activity

Traditionally, *S. birrea* has been used for treating hypertension. *S. birrea* effect on arterial BP in rats distressed with hypotonic solution exhibited dose-dependent reduction in BP. It showed hypotensive effect intercede *via* influence on cardiovascular components (Gondwe et al., 2008). Another report showed aqueous bark extract of *S. birrea* on normal and hypertensive Dahl salt-sensitive rats exhibited antihypertensive effect in aortic rings. The hypotensive effect of *S. birrea* was induced by the reduced concentration of endothelium synthesized nitric oxide (Ojewole, 2006).

10.3.8 Anticonvulsant Activity

The bark aqueous extract of *S. birrea* exhibited anticonvulsant activity in mice induced with seizures using picrotoxin, pentylenetetrazole (PTZ) and bicuculline. It inhibited chemically induced seizures as compared with the reference anticonvulsant drugs diazepam and phenobarbital (Ojewole, 2007).

10.3.9 Contractile Effect

The leaf aqueous extract of *S. birrea* exhibited a contractile effect in vascular smooth muscle isolated from rat and rabbit. The mechanism of action of vasoconstriction might have been mediated *via* endothelin-1 and prostaglandins (endothelium-derived vasoconstrictors), the extracellular Ca^{2+} influx and intracellular Ca^{2+} release (MAwOzA et al., 2012). Traditionally in Nigeria, *S. birrea* has been used to induce childbirth. A report on *S. birrea* showed contractile effect in myometrial smooth muscle cells as a validation for Nigerian ethnomedicine to facilitate childbirth (Attah et al., 2012).

KEYWORDS

- **anacardiaceae**
- ***Escherichia coli***
- **pharmacology**
- **phytosterols**
- ***Sclerocarya birrea***
- **triterpenoids**

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CHAPTER 11

Bioactives and Pharmacology of *Tribulus terrestris* L.

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11.1 INTRODUCTION

Tribulus terrestris L. is an annual plant that belongs to the family Zygophyllaceae and is popularly known as ‘Puncture vine’ or ‘Devil’s horn.’ The plant is a small, prostrate 10–60 cm, hirsute or silky hairy herb with opposite, unequal, paripinnate leaves, leaflets 5–8 pairs, and elliptical or oblong-lanceolate. The fruits have five mericarps, which are ax-shaped, 3–6 mm long, arranged radially with a diameter of 7–12 mm, and have a hard texture. *T. terrestris* can thrive in desert climates and poor soil. *T. terrestris* is widely distributed in Africa, Western Asia, China, Japan, Korea, and Europe. The plant is commonly referred to as ‘Caltrop,’ ‘Goat head,’ ‘Bull’s head,’ and ‘Ground burr nut’ in English. *T. terrestris* has various vernacular names such as *Bhakra* (Punjabi), *Ci ji li* (Chinese), *Chotagokhru* (Hindi), *Neringil* (Malayalam), *Ghokaru* (Marathi), *Ghokshura* (Sanskrit), *Nerunjimullu* or *Sirunerunji* (Tamil), *Palleru* (Telugu), and *Gokharu* (Urdu).

The plant has been widely used in folk medicines to treat impotence, rheumatism, hypertension, and kidney stones (Pavin et al., 2018). The plant also provides protection against oxidative stress and exhibits antitumor, cytotoxic, antifungal, anti-helminthic, anti-diabetic, anti-hypertensive properties. Fruits are very effective in the treatment of genito-urinary tract disorders. It has been used traditionally in Indian (ITM) and Chinese Traditional Medicine (CTM) as an Aphrodisiac. The aerial part has been used to treat hormonal imbalance, sexual disorders, cardiovascular diseases (CVDs), kidney, and skin disorders (Semerdjieva and Zheljazkov, 2019). It is a vital constituent of “Gokshurandi Guggul,” a potent Ayurvedic medicine used for the proper functioning of the genito-urinary tract and to remove kidney stones. The Ayurvedic Pharmacopoeia of India attributes cardiogenic properties to the root and fruit. In Chinese medicine, the fruits are used for the treatment of eye trouble, edema, abdominal distension, leucorrhea, and sexual dysfunction (Chhatre et al., 2014). The plant has been used as a folk medicine in Iraq as tonic, aphrodisiac, analgesic, astringent, stomachic, diuretic, lithotriptic, and as a urinary anti-infective (Pandey, 2014).

Wang (1989) and Hashim et al. (2014) gave a detailed review on phytochemistry and pharmacology of *Tribulus terrestris*.

11.2 BIOACTIVE COMPOUNDS

Phytochemical investigations of *T. terrestris* showed the presence of various chemical compounds such as steroidal saponins, flavonoids, glycosides, phytosterols, tannins, terpenoids, and amide derivatives. Among them, steroidal saponins and flavonoids were considered to be the major bioactive compounds. The plant contains 58 different spirostane saponins and 50 furostane saponins. Protodioscin and protogracilin, kind of steroidal saponins were found to confer unique biological activities. Alkaloids obtained from *T. terrestris* were mainly the derivatives of quercetin, kaempferol, and isorhamnetin. Tribulusamide C, tribulusterine, tribulusin A, harmine, harman, harmol, tribulisimide C, terrestriamide, N-transcoumaroyltyramine, N-trans caffeoyltyramine, terretribisamide (Table 11.1).

Other organic acids such as benzoic acid, vanillic acid, 2-methoxy benzoic acid, ferulic acid, palmitic acid, monoglyceride, succinic acid, docosanoic acid, tribulis acid were also identified. Alanine and threonine were the major amino acids also found. In addition, *T. terrestris* also contains 4-ketopin-oresinol, uracil nucleic acid, coumarin, emodin, and physcion (Figure 11.1) (Zhu et al., 2017).

TABLE 11.1 Details of the Chemical Compounds Found in *Tribulus terrestris* L. and its Pharmaceutical Properties

SL. No.	Bioactive Compound	Property	References
1.	Quercetin	Anti-urolithic activity	Sharma et al. (2017); Arasaratnam et al. (2010)
2.	Diosgenin	Anti-urolithic activity	Sharma et al. (2017); Arasaratnam et al. (2010)
3.	Tannic acid	Anti-urolithic activity	Sharma et al. (2017); Arasaratnam et al. (2010)
4.	Tribulosin	Antihelmintic activity	Deepak et al. (2002)
5.	Sitosterol glucoside	Antihelmintic activity	Deepak et al. (2002)
6.	N-trans-p-caffeoyl tyramine	Anti-inflammatory	Ko et al. (2015)
7.	Protodioscin	Aphrodisiac activity	Zhu (2011)
8.	Spirostane saponins	Treatment of infertility and libido disorders in men and women	Kostova and Dinchev (2005)
9.	Furostane saponins	Treatment of infertility and libido disorders in men and women	Kostova and Dinchev (2005)
10.	Protogracilin	Aphrodisiac activity	Zhu (2011)
11.	Kaempferol	Anticancer Anti-inflammatory Antioxidant Anti-diabetic Cardioprotective Neuroprotective Anti-osteoporotic Estrogenic/anti-estrogenic Analgesic Anxiolytic Anti-allergic	Calderon et al. (2011)
12.	Isorhamnetin	Anticancer Anti-inflammatory Antioxidant Antiviral Antimicrobial	Kandakumar and Manju (2017)
13.	Tribulusamide C	Anti-inflammatory	Semerdjieva and Zheljakov (2019)

TABLE 11.1 (Continued)

SL. No.	Bioactive Compound	Property	References
14.	Tribulusterine	Neuroprotective	Bremner et al. (2003)
15.	Harmin	Anticancer Anti-inflammatory Antimicrobial Antiparasitic Anti-HIV	http://flipper.diff.org
16.	N-transcoumaroyl-tyramine	Anticancer Antioxidant Anti plateletic	Kim and Lee (2003)
17.	N-trans-p-caffeoyl tyramine	Anti-inflammatory	Ko et al. (2015)
18.	Terrestribisamide	Antioxidant Antimicrobial Cytotoxic activity	Raj et al. (2013)
19.	Vanillic acid	Anti-inflammatory	Calisto-Campos et al. (2015)
20.	Ferulic acid	Antioxidant	Zdunska et al. (2018)
21.	Docosanoic acid	Tumor suppression	Iijima et al. (2006)
22.	Emodin	Anticancer	Yang et al. (2013)

11.3 PHARMACOLOGY

11.3.1 Aphrodisiac Activity

T. terrestris consists of active extracts and constituents which could effectively improve sexual function through activating aphrodisiac and improves fertility in men. *T. terrestris* has the ability to increase testosterone or testosterone precursor levels (Neychev and Mitev, 2016).

11.3.2 Improvement in Fertility

T. terrestris influences spermatogenesis by increasing the total tube length, tubular volume, and height of the seminiferous epithelium (Oliveira et al., 2015).

Chemical compounds found in *Tribulus terrestris*

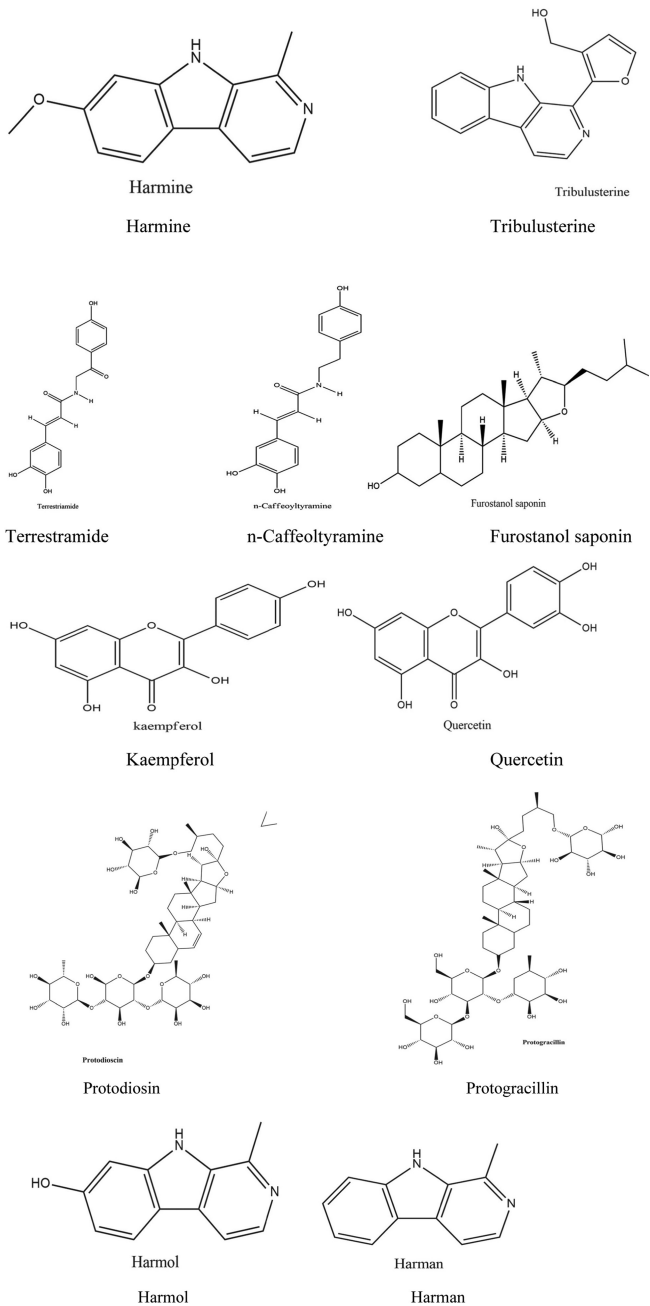


FIGURE 11.1 Chemical compounds found in *Tribulus terrestris*

11.3.3 Libido-Enhancing Activity

T. terrestris treatment (250 mg orally three times a day for 90 days) was considered to be effective in treating sexual problems among menopausal women (Postigo et al., 2016).

11.3.4 Anti-Urolithic Activity

The aqueous extracts of *T. terrestris* fruits has been traditionally used to treat various urinary infections including Urolithiasis. The presence of Quercetin, diosgenin, and tannic acid in the extract has a protective capacity rather than curing urolithiasis (Sharma et al., 2017). The oral administration of *T. terrestris* extract drastically reduced the levels of citrate, oxalate, proteins, and glycosaminoglycan in patients' 24 h urine samples. Thus, *T. terrestris* extract is useful in the treatment of urolithiasis (Arasaratnam et al., 2010).

11.3.5 Antidiabetic Activity

The gross saponin extract of *T. terrestris* (GSTT) showed inhibitory activity against α -glucosidase and inhibited postprandial increase in blood glucose. Improvement in insulin dependent diabetes symptoms were also reported (Ercan and El, 2016).

11.3.6 Role in Cardiovascular Diseases (CVDs)

GSTT obtained from *T. terrestris* plays a vital role in the treatment of cardiovascular disease with anti-myocardial ischemia and myocardial ischemia-reperfusion injury. GSTT reduced the levels of lactate dehydrogenase (LDH), methane dicarboxylic aldehyde (MDA), tumor necrosis (TNF- α) and Interleukin (IL-6), increased SOD and the rate of apoptosis and also improved the structure of cardiomyocytes in rats. In addition, GSTT could improve coronary flow of heart function and increase adenosine triphosphate (ATP) in myocardial ischemia-reperfusion injury (Jiang et al., 2011).

11.3.7 Neuronal Cells Protective Activity

T. terrestris has anti-inflammatory of antioxidant effects. GSTT reduced the damage to FC12 cells caused by H₂O₂ by increasing the membrane potential

of mitochondria and BCL-2 protein expression in PC12 cells, in dosage-dependent manner (Jiang et al., 2008). The intravenous administration of *T. terrestris* powder can reduce the degeneration of retinal Ganglion cells (RGC's) and retinal nerve fiber layer in hyper-intraocular pressure in rabbits (Sheng and Meng, 2007).

11.3.8 Anti-Tumor Activity

GSTT has the ability to enhance apoptosis and inhibit metastasis in breast cancer cell lines. GSTT was found to reduce the expression of CXCR4 (Overexpression of CXCR4 causes metastasis) in MCF-7 cells (Goranova et al., 2015). GSTT also prevents UVB induces carcinogenesis. This effect is due to the enhancement of NER gene expression and by blocking UVE mediated NF-kB activation (Sisto et al., 2012).

11.3.9 Antioxidant Activity

The butanol extract (1 mg ml⁻¹) *T. terrestris* was rich in saponin, which had quenching activity of nitric oxide (90.30%), hydroxyl radicals (90.02%) and hydrogen peroxide radicals (89%) (Hemalatha and Hari, 2013). *T. terrestris* also has 2,2 di (4-tert-octylphenol)-1 picrylhydrazyl (DPHH), H₂O₂ and superoxide scavenging activities in a dose dependent manner. Diosgenin, an active bioactive compound, obtained from the callus of *T. terrestris* was reported (Bhuvad and Nishteswar, 2016).

11.3.10 Absorption Enhancer

Metformin hydrochloride (HCl) is a biopharmaceutics classification system class III drug which has high solubility and poor absorption characteristics. *T. terrestris* can enhance the absorption of metformin HCl in a goat intestine. This enhanced absorption effect was due to excess of saponins in *T. terrestris* (Prabhu and Hadigal, 2014).

11.3.11 Anti-Bacterial Activity

The ethanolic and aqueous extract of *T. terrestris* showed anti-bacterial activity against both gram positive and gram-negative organisms like *Bacillus*

subtilis, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Shigella flexneri* (Pandey, 2014).

11.3.12 Anti-Helminthic Activity

The methanolic extract of *T. terrestris* showed anti-helminthic activity against using the nematode *Caenorhabditis elegans*. This is due to the presence of bioactive compounds tribulosin and sitosterol glucoside in *T. terrestris* (Deepak et al., 2002).

11.3.13 Larvicidal Activity

The petroleum ether extract of *T. terrestris* exhibited larvicidal activity against the third instar larvae and adults of the mosquito, *Aedes aegypti*, the vector of dengue fever (Oliveira et al., 2015; Kumari and Singh, 2015).

11.3.14 Anti-Inflammatory Activity

N-trans-p-caffeoyl tyramine isolated from *T. terrestris* and methanolic extract had anti-inflammatory activities. N-trans-p-caffeoyl tyramine suppressed the expression of cyclooxygenase (COX)-2 and prostaglandin E2 (PGE2) by decreasing the expressions of p-JNK (Ko et al., 2015).

11.3.15 Hepatoprotective Activity

GSTT can heal the injured liver cells and have a protective effect on acute hepatic injury in mice induced by Tripterygium glycosides. The hepatoprotective mechanism may be due to the antioxidant activity, regulation on metabolism regulation, expression of apoptosis of liver cells, which ultimately reduce the level of caspase-3 in liver tissues (Hu, 2009).

11.3.16 Anticaries Activity

T. terrestris inhibited *Streptococcus mutants*, an important oral pathogen that causes dental caries. *T. terrestris* extract suppressed the adherence of

Streptococcus mutants to saliva-coated hydroxyapatite (S-HA), which stimulated teeth and inhibited the formation of water-insoluble glucans (Oh et al., 2011).

11.3.17 Antiaging and Memory Improvement Activity

GSTT significantly improved memory disorder and recovered memory disorder (Zhang et al., 2007). GSTT can effectively increase SOD activity in the skin and showed a thicker dermis and more compactly arranged fiber content (Zhu, 2011).

KEYWORDS

- ***Tribulus terrestris***
- **gross saponin extract of *T. terrestris***
- **interleukin**
- **lactate dehydrogenase**
- **methane dicarboxylic aldehyde**
- **retinal ganglion cells**
- **tumor necrosis**

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CHAPTER 12

Phytochemistry and Pharmacological Properties of *Ichnocarpus frutescens* W. T. Aiton

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12.1 INTRODUCTION

Ichnocarpus frutescens W. T. Aiton, known as the black creeper, is a flowering plant from the family Apocynaceae found all over India. It is a creeper found in high-altitude areas and mostly in deciduous forests and some plains. In Indian Ayurveda, it is a substitute for *Hemidesmus indicus* as a folk medicine that has various activities against numerous diseases. It is also used traditionally in formulations for reducing fever and rashes in the skin (Ashutosh et al., 2009). *Decalepis hamiltonii*, *Cryptolepis buchananii*, *Ichnocarpus frutescens*, and *Hemidesmus indicus* are sold in the local crude drug market with the tag Sariva, which is traditionally given to pregnant women to secure their fetal growth who tend to go for abortion (Singh and Singh, 2012). The leaves of the plant are entire, elliptic-oblong to broadly lanceolate, acute or acuminate, leaf base is usually rounded, glabrous above, and pubescent beneath with

4–6 pairs of lateral nerves. The flowers are fragrant with a greenish-white or purplish color, with the seeds being linear, long, and black. This review aims to study the underlying phytochemicals and pharmacology of this plant.

12.2 BIOACTIVES

The biochemical analysis of the plant *I. frutescens* shows that it is a phytochemical-rich species with a wide variety of compounds. Numerous analyzes show that the plant contains polyphenols, terpenoids, alkaloids, phytosterols, carbohydrates, coumarins, glycosides, and flavonoids. Studies show that the leaves of *I. frutescens* possess a higher percentage of carbohydrate content with 3.58% as compared to stem which has 3.04% and root which has 2.28% (Ashutosh et al., 2009). Some of the notable carbohydrates present in the extract of plants are α -L-sarabopyranoside, 6,8, 8, trimethylpentacosan-7-one, α -amyirin and α -L-rhamnopyranosyl-(1 \rightarrow 4)- β -D-glucopyranosyl-(1 \rightarrow 3)- α -amyirin. Lipids such as fatty acids including n-butyl oleate, cholesterol-like β -sitosterol and benzocosanyl arachidate are also present in the plant. Hydrocarbons and their derivatives are abundant in the plant material n-octyltetracontane, tetratriacontadiene, and n-nonadecanyl benzoate (Aggarwal et al., 2010). Triterpenoids are abundant throughout the plant such as α -L-rhamnopyranosyl-(1 \rightarrow 4)- β -D-glucopyranosyl-(1 \rightarrow 3)- α -amyirin, α -amyirin, lupeol, friedelin, epi-friedelinol, and oleanolic acid. Polyphenols such as quercetin-3-O- β -D-glucopyranoside, sinapic acid, protocatechuic acid, ferulic acid, caffeic acid, apigenin, vanillic acid, syringic acid, luteolin, ursolic acid, kaempferol, kaempferol-3-galactoside (trifolin), mannitol, vitexin, isovitexin, and proanthocyanidin are also present in the plants (Kumarappan et al., 2015). In the chloroform extract of the plant, a new novel compound called carpuside which was deduced as calogenin-3-O- α -L-fucopyranosyl-(1 \rightarrow 4)- α -L-digitoxopyranoside was found (Srivastava et al., 2017). The structures of some of the significant phytochemicals present in *I. frutescens* were drawn using ACD/ChemSketch (version 2020.2.0) and shown in Figure 12.1.

12.3 PHARMACOLOGY

12.3.1 Antioxidant Activity

The polyphenolic extract (PPE) of *I. frutescens* was subjected to DPPH free radical scavenging activity, which showed a higher radical scavenging activity than the control α -tocopherol, which has a IC_{50} of 142.91 μ g/mL

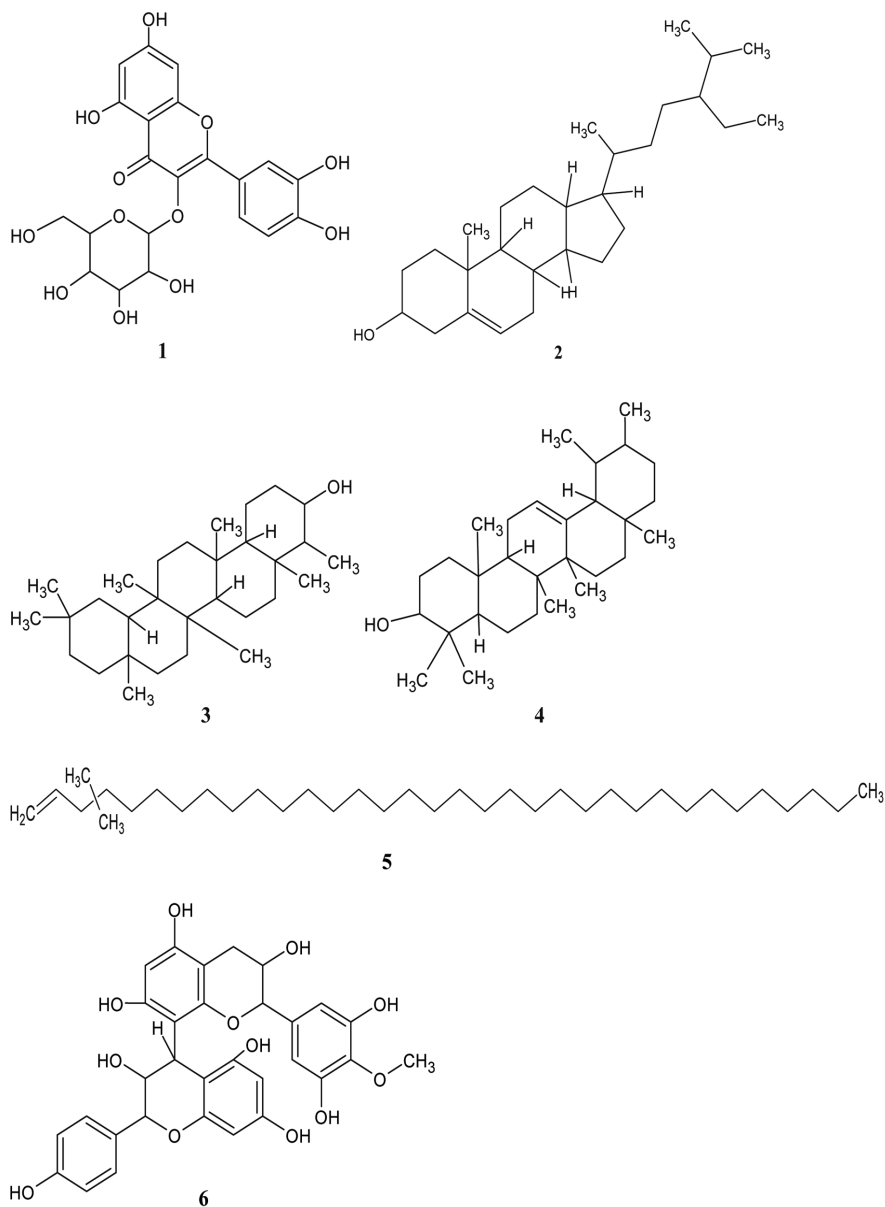


FIGURE 12.1 2D structure images of quercetin-3-O- β -D-glucopyranoside (PubChem CID 12304324) (1); β -sitosterol (PubChem CID 222284) (2); epi-friedelinol (PubChem CID 101341) (3); α -amyrin (PubChem CID 73170) (4); tetratriacontadiene (PubChem CID 71421063) (5); and proanthocyanidin (PubChem CID 108065) (6).

whereas the polyphenol extract with IC_{50} 163.38 $\mu\text{g/ml}$ (Kumarappan et al., 2012). Super oxidase dismutase (SOD) of *I. frutescens* activity on the paracetamol (PCM) induced rats showed an increase in the SOD levels when the concentration is increased and also exhibiting hepatoprotective activity on the cells (Dash et al., 2007). Hydro alcoholic extract (HAE) of *I. frutescens* was used for calculating the antioxidant activity using hydrogen peroxide scavenging potential. The IC_{50} value of HAE was found out to be 167.46 mg/ml (Kumarappan and Mandal, 2007).

12.3.2 Antibacterial Activity

Considering the other subject of study, chloroform extract of *I. frutescens* showed antibacterial activity against *Bacillus pumilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *P. putida*, and *Proteus* sp. (Malathy and Sini, 2009). Aqueous extract of the stem and leaf of *I. frutescens* showed effective bactericidal property against *Bacillus subtilis* and *Escherichia coli*, whereas in the methanol extract of stem and root, only root extract depicted activity against both the organisms and the stem extract only showed activity against *Bacillus subtilis* (Daisy et al., 2012). The antibacterial activity of *I. frutescens* was studied by filter paper disc diffusion assay on *Bacillus pumilis* and *Escherichia coli* using hexane, chloroform, and water extracts. Only the chloroform extract of *I. frutescens* showed considerable inhibition on *Bacillus pumilis* and *Escherichia coli* (Sini and Malathy, 2006). Ethanolic extract of rhizomes of *I. frutescens* showed antibacterial activity against both gram-negative bacteria-*Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhimurium* and gram-positive-*Staphylococcus aureus* and *Bacillus subtilis* exhibiting broad-spectrum antibacterial activity (Angle and Sardessai, 2017).

12.3.3 Antifungal Activity

The antifungal activity of the crude chloroform extracts of *I. frutescens* roots by the disk diffusion method showed zone of inhibition (ZI) against *Aspergillus flavus*, *A. fumigatus*, *A. niger*, *A. terreus*, *Cladosporium oxysporum*, *Penicillium candidum*, *P. pergenum* and *Trichoderma viride*. It is also shown that the ZI increased with increase in concentration in *Aspergillus* sp. (Malathy and Sini, 2009). Ethanolic extracts of roots of *I. frutescens* exhibited a significant antifungal effect against *Candida albicans* but no antifungal activity against *Aspergillus niger* (Angle and Sardessai, 2017).

12.3.4 Wound Healing Activity

The ethanolic extract of the roots of *I. frutescens* made into an ointment base with an extract concentration of 1% and 2% w/w was applied into the excision and incision wound models in rats showed significant wound healing properties when compared to the control drug standard framycetin sulfate cream (Pandurangan et al., 2008). Excision wounds created on the rat models were treated with HAE of stem, leaves, and roots separately. The study showed that the extracts show very higher wound healing activity than the standard povidone-iodine. Among which the extract of stem was the most effective where the wound was completely healed in 14 days (Meher, 2013).

12.3.5 Anti-Inflammatory Activity

Carrageenan induced rat paw edema was used in analyzing the anti-inflammatory activity of the methanolic extract of *I. frutescens*. Intra-plantar injection of carrageenan in the hind paw was used to induce a gradual increase in the edema paw volume in the rats. Extracts at doses of 100, 200 and 300 mg/kg significantly inhibited the edema formation of rat paw when compared with the standard drug indomethacin (Pandurangan et al., 2008). Hydroalcoholic extract (HAE) of *I. frutescens* *in vivo* anti-inflammatory effects assayed by using carrageenan, dextran induced paw edema and cotton pellet granuloma methods show significant results with the highest concentration of HAE administered to the rats. HAE at a concentration of 300 mg/ kg dosage gave 33.10%, 30.13%, and 39.85% reduction of carrageenan, dextran induced paw edema and cotton pellet granuloma, respectively in the rat models (Kumarappan et al., 2006).

12.3.6 Antihyperglycemic Activity

Active fraction of methanolic extract of *I. frutescens* at a dose of 50 mg/kg body weight in albino mice exhibited significant antihyperglycemic activity, evidently with reduced blood glucose level up to 58.84%, which is due to the regeneration of pancreatic β -cells and a significant improvement in serum lipid profile (Srujana et al., 2018). In streptozotocin (STZ)-nicotinamide induced type-II diabetic rats, the aqueous extract of *I. frutescens* with a dosage of 250 mg/kg and 500 mg/kg showed a significant fasting glucose levels on the 10th and 15th days with an increased glucose tolerance (Barik et al., 2008).

12.3.7 Antitumor Activity

Kumarappan and Mandal (2007) studied the PPE of the leaves of *I. frutescens* by evaluating it for the antitumor activity *in vivo* using the Murine Ehrlich ascites carcinoma (EAC) model and *in vitro* using the U-937 monocytoid leukemia and K-562 erythroleukemia cell lines and the results proved that *I. frutescens* possesses strong free radical scavenging activity and antitumor activity. Dash et al. (2007) investigated experimentally the possible antitumor activity and antioxidant role of *I. frutescens* in the mice transplanted with EAC. The chloroform and methanol extract of the whole plant were administered intraperitoneally, and they exhibited significant antitumor and antioxidant activity. *In vitro* anticancer activity of the residue from methanolic extract of roots of *I. frutescens* and isolated triterpenes were evaluated by MTT assay using MCF-7, BEL-7402, SPC-A-1 and SGC-7901 cancer cell lines and it showed significant anticancer activity on the four cancer cell lines (Singh and Singh, 2014). Starlin et al. (2013) evaluated the protective effect of *I. frutescens* against 4-vinyl cyclohexane induced ovarian cancer in Swiss albino mice and concluded that the ethanolic extracts of *I. frutescens* W. T. Aiton have effective anticancer activity.

12.3.8 Hepatoprotective Activity

Hepatoprotective activity of PPE of leaves of *I. frutescens* against CCl_4 and tamoxifen-induced hepatotoxicity in rats was studied. The PPE showed a significant increase in reduced glutathione (GSH) levels and a decrease in serum enzyme levels. The histopathological studies also reveal that the liver tissues had less damage (Kumarappan et al., 2016). PCM induced acute liver damage to the albino rats was used in the study of the hepatoprotective activity against chloroform and methanol extract of *I. frutescens*. The serum hepato-specific markers' activity was used in the determination of the hepatoprotective activity. The extracts showed comparable results with the standard drug Silymarin (Dash et al., 2007).

12.3.9 Insecticidal Activity

The hexane, diethyl ether, dichloromethane, and ethyl acetate (EtOAc) extracts of the leaf of *I. frutescens* was used in testing the larvicidal activity of *Culex quinquefasciatus* (*Cx. quinquefasciatus*), a pantropical pest. It was

shown that only the hexane extract of *I. frutescens* had effective larvicidal activity against the *Culex quinquefasciatus* (Tennyson et al., 2012). The oviposition activity of the leaf extract of *I. frutescens* with hexane, dichloromethane, and EtOAc showed positive activity against the third instar larvae of *Spodoptera litura* (Arivoli and Tennyson, 2013).

12.3.10 Anti-Urolithiatic Activity

EtOAc root extract of *I. frutescens* in nephrolithiasis-induced rats was used for the anti-urolithitic activity. The rat models were fed with ethylene glycol water for 28 days, which resulted in hyperoxaluria and in the increased renal excretion of Ca and P. Also, the deposition of stone-forming materials was reduced significantly after the administration of EtOAc root extract (Deepak et al., 2007).

12.3.11 Analgesic Activity

Hot plate and tail immersion methods were used to check the analgesic activity of 70% alcoholic extract of leaves, stems, and roots of *I. frutescens* in Wistar rats. At a dosage of 500 mg/kg, the extract showed a higher percentage of protection with 154.12% in the hot plate method and 221.33% in the tail immersion method with the stem extract (Mishra et al., 2009).

KEYWORDS

- apocynaceae
- *Cryptolepis buchananii*
- Ehrlich ascites carcinoma
- hydroalcoholic extract
- *Ichnocarpus frutescens*
- polyphenolic extract
- super oxidase dismutase

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CHAPTER 13

Chemical Diversity of Bioactive Molecules and Therapeutics of *Dodonaea viscosa* (L.) Jacq.

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13.1 INTRODUCTION

Dodonaea viscosa (L.) Jacq. (Syn.: *D. viscosa* subsp. *angustifolia*, *D. angustifolia*) belongs to an angiosperm family Sapindaceae. It is a flowering evergreen woody perennial shrub. The common name of *D. viscosa* is hopbush, but different common names are used in different areas which contain narrow-leaf hopbush, broadleaf hopbush, native hop bush, switchsorrel, candlewood, vassoura-docampo, vassoura-vermelha, vassoura-vermelha, Gansies, Dodanaia, Kankerbos, Daidon, Sanatha, and Shath (Kaigongi et al., 2020; Akhtar et al., 2011). *D. viscosa* is a native plant of Australia, but then it is widespread all over the subtropics and tropics. It is generally dioecious-rarely monoecious, large, profusely branched medium to tall shrub with brownish, cracked long thin striped bark. Leaves simple, spiral, alternate, twig ends are clustered; petiole 0.2 cm, stout, base is swollen, narrow elliptic to oblanceolate, apex apiculate tip at acuminate, decurrent base, intact margin and revolute, glabrous surface, viscid; midrib raised above. Terminal or axillary paniced cymose inflorescence, up to 7 cm long. Small greenish pedicellate flowers with imbricate or valvate sepals; petals absent; stamens 6–8, ovary triquetrous, stigma trifid. Fruit capsule, compressed, membranous, with 3 wings; seeds black, 1–2. Flowering period January to March. Traditionally, *D. viscosa* is used in treating skin infections, diarrhea,

rheumatism, stomachaches, hepatic pain, uterine colic and other ailment concerning smooth muscles, dermatitis, sore throat, and hemorrhoids. The leaves leaven is helpful to treatment of fractures, rheumatism, hemorrhoids, snake bites, and gout. Root extract is used against common cold, seeds with honey are effective to cure malaria (Abdela, 2019; Meenu et al., 2011; Rajamanickam et al., 2010; Rojas et al., 1992, 1996).

Anilreddy (2009), Rajeswari et al. (2011) and Al-Snafi (2017) reviewed the phytochemistry and pharmacology of *Dodonaea viscosa*.

13.2 BIOACTIVES

The initial phytochemical screening of *D. viscosa* exposed that it contained flavonoids, carbohydrates, steroids, phenolic, cardiac glycosides, alkaloids, saponins, gums, tannins, coumarins, mucilages, and others trace elements (Jawahar et al., 2004; Venkatesh et al., 2008; Khurram et al., 2011; Ramya et al., 2011; Riaz et al., 2012; Ramamurthy et al., 2013; Kumar et al., 2013; Jeya et al., 2014; Shafek et al., 2015; Al-Azawi, 2016; Anode et al., 2018; Orpin et al., 2018; Abdela, 2019; Hossain, 2019).

Antioxidants agents were isolated by using *D. viscosa* leaves extract such as Penta hydroxyflavane and 4-methoxylstigmasterol (Al-Habsi and Hossain, 2018). Several antioxidant compounds have been detaching from leave, fruit, stem of *D. viscosa* (Akthar et al., 2016). Neo-Clerodane diterpenoids, clerodane diterpenoids, and Isoprenylated flavonoids were isolated from *D. viscosa* (Gao et al., 2013; Omosa et al., 2010). Biologically active C-alkylated five potent compounds were reported from *D. viscosa* given in Figure 13.1 (Akthar et al., 2012). Polyphenolic nine compounds have been isolated by using *D. viscosa* methanolic aerial parts extract presented in Figure 13.2 (Uddin et al., 2018). Structures of seven hautriwaic lactone compounds given in Figure 13.3 (Akthar et al., 2016). Six compounds of triterpenoids have been isolated from *D. viscosa* presented in Figure 13.4 (Wang et al., 2018). Three compounds of Cyclopropylclerodanes such as Dodovisate C given in Figure 13.5, have been isolated from *D. viscosa* (Marvilliers et al., 2020).

Contained water-soluble polysaccharide involved of D-glucose and D-mannose in 5:2 molar ratios were found in seeds of *D. viscosa*. The investigation of the component monosaccharides specified β -linkages in D-mannopyranose units and α -linkages in D-glucopyranose and (Singh et al., 1992).

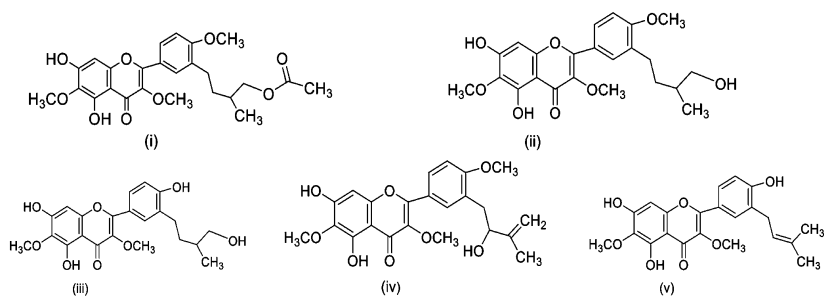


FIGURE 13.1 (i) C-alkylated flavonoid (5,7-dihydroxy-3'-(4''-acetoxy-3''-methylbutyl)-3,6,4'-trimethoxyflavone, (ii) (5,7-dihydroxy-3'-(3-hydroxymethylbutyl)-3,6,4'-trimethoxyflavone, (iii) 5,7,4'-trihydroxy-3'-(3-hydroxymethylbutyl)-3,6-dimethoxyflavone, (iv) (5,7-dihydroxy-3'-(2-hydroxy-3-methylbutenyl)-3,6,4'-trimethoxyflavone, (v) 5,7,4'-trihydroxy-3,6-dimethoxy-3'-isoprenyl-flavone.

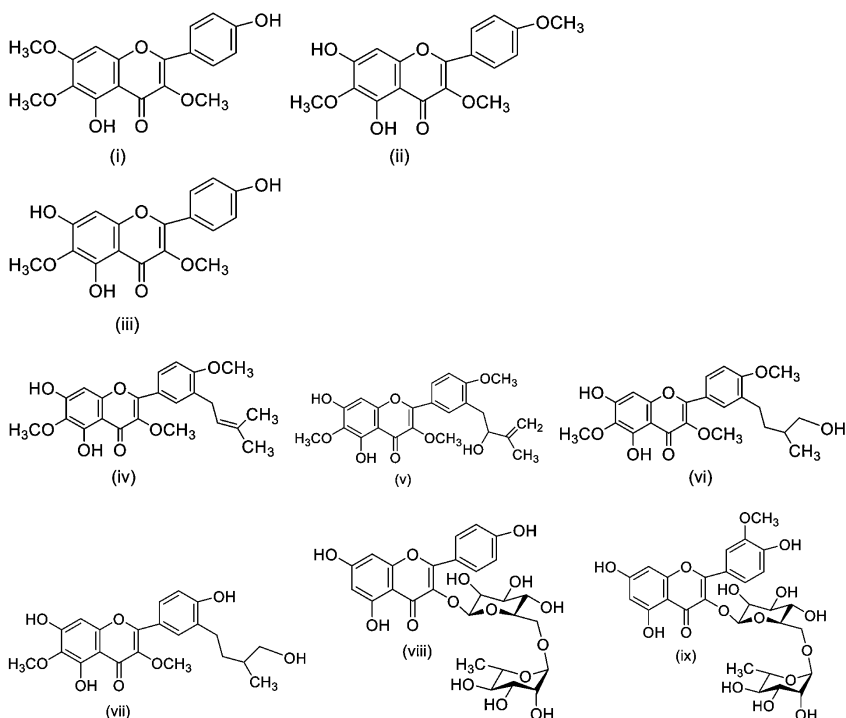


FIGURE 13.2 (i) Penduletin, (ii) 5,6-dihydroxy-3,4',7-trimethoxyflavone, (iii) Viscosine, (iv) Viscosol, (v) 5,7-dihydroxy-3'-(2-hydroxy-3-methylbutenyl)-3,6,4'-trimethoxyflavone, (vi) 5,7-dihydroxy-3'-(3-hydroxy-methylbutyl)-3,6,4'-trimethoxyflavone, (vii) 5,7,4'-trihydroxy-3,6-dimethoxy-3'-isoprenyl-flavone, (viii) Kaempferol and (ix) 3-O-rutinoside Isorhamnetin-3-O-robinobioside

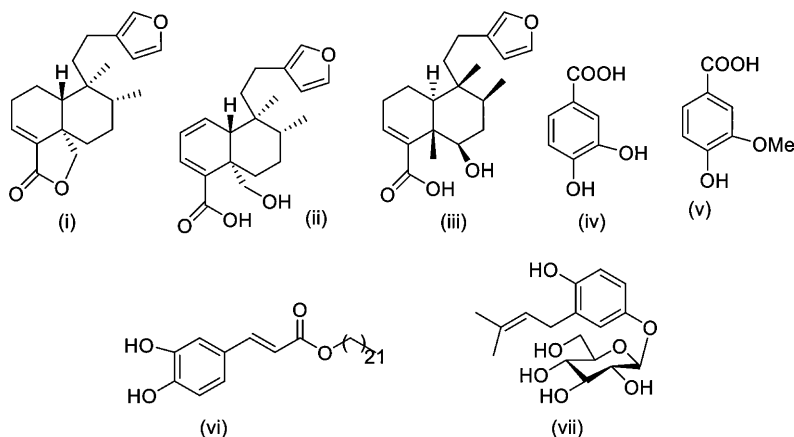


FIGURE 13.3 Structures of Hautriwaic lactone (i); 6 β -hydroxy-15,16-epoxy-5 β ,8 β ,9 β ,10 α -cleroda-3,13 (16), 14-trien-18-oic acid (ii); 3,4-dihydroxybenzoic acid (iii); vanillic acid (iv); nebrodenside (v); docosyl caffeate (vi); and 15,16-epoxy-19-hydroxy-1,3,13-(16),14-clerodatetraen-18-oic acid (vii); (Akthar et al., 2016).

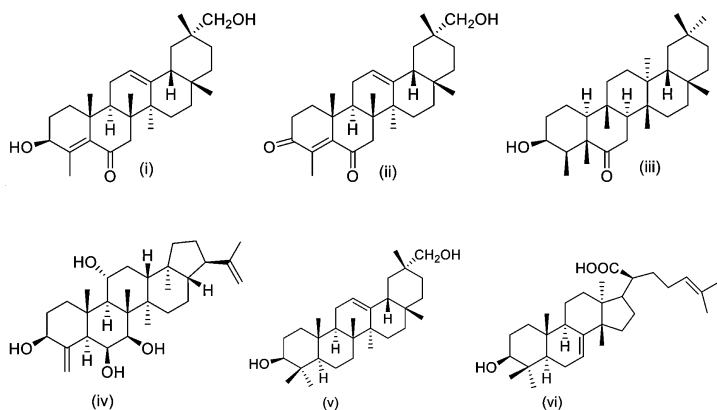


FIGURE 13.4 Structures of triterpenoids 6-oxo-24-nor-4,12-oleanadien-3 β ,29-diol (i), 3,6-dioxo-24-nor-4,12-oleanadien-29-ol (ii), Epifriedelinol (iii), Cavalerol A (iv), Olean-12-ene-3 β ,29-diol (v) and 3 α -hydroxytirucalla-7,24-dien-21-oic acid (vi).

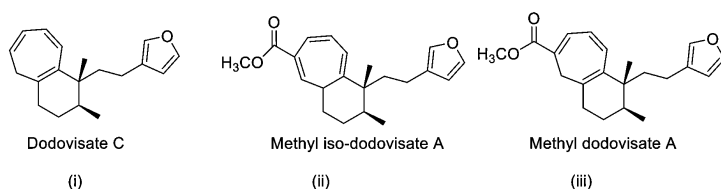


FIGURE 13.5 Structure of the three cyclopropylclerodanes Dodovisate C (i) Methyl iso-dodovisate A (ii) Methyl dodovisate A (iii). (Reprinted with permission from Marvillers et al., 2020. <https://creativecommons.org/licenses/by/4.0/>)

13.3 PHARMACOLOGY

13.3.1 Anti-Viral Activity

Ethanollic extracts of *D. viscosa* aerial parts were used to herpes simplex virus type 1 (HSV-1) for tested of *in vitro* antiviral activity (Oliveira et al., 2012). Different extracts of *D. viscosa* were tested syncytia formation assay was used for anti-HIV-1 activity (Rashed et al., 2013). Solvent leaves extract of *D. viscosa* were used to measure *in vitro* antiviral effect against RV SA-11 and CVB3 (Shaheen et al., 2015). *D. viscosa* extract was active *in vitro* on herpes simplex HSV-1 (Zhang et al., 2016).

13.3.2 Antimicrobial Activity

The methanol, chloroform, and aqueous extracts of stem, root, and leaf of *D. viscosa* were examined inhibitory effects against *Vibrio cholerae*, *Bacillus subtilis*, *Escherichia coli*, *Proteus mirabilis*, *Curvularia lunata*, *Penicillium citrinum*, *Aspergillus flavus*, and *Fusarium oxysporum* (Kannaian et al., 2012). different solvent extracts of *D. viscosa* leaves were examined anti-microbial activity. *In-vitro* by agar diffusion method against some selected microbial strains (Al-Bimani and Hossain, 2020). *D. viscosa* methanolic leaves extract was used against *Streptococcus mutans*. After 6 h, the extract of *D. viscosa* destroy 100% of *S. mutans* at 25 mg/ml and 0.1 mg/ml killed 45% (Naidoo et al., 2012). The ethanolic and aqueous extracts of *D. viscosa* possesses anti-salmonella effects; agar well and disc diffusion methods were used. In disc diffusion assay, ethanol extract (71.19%) showed better result as compared to aqueous extract (28.81%). On the other hand, in the well diffusion method distilled water extract (52.54%) showed the lowest concentration than ethanol extract (88.13%) (Al-baker et al., 2014).

D. viscosa extracts are active by selected microorganism ethanolic extract showed MBC's against *S. aureus* was 256 µg/ml. The MIC's against *S. aureus* (NCIMB 6571) was 64 µg/ml (Khurram, 2010).

D. viscosa extract was used against antimicrobials. It was observed that extract of *D. viscosa* leaves possesses antibacterial profile by using some selected microorganism (*Staphylococcus aureus* and *Streptococcus pyogenes*) effective activity against influenza and Coxsackie virus. In comparison, the extract did not exhibit antifungal activity (Getie, 2003). *D. viscosa* showed antibacterial activities against selected microorganisms (*Escherichia coli*, *Micrococcus luteus*, *Salmonella typhi*). The extract showed MICs within

the different range from 5 to 20.0 mg/mL (Khurram et al., 2009). Ethanolic and diethyl ether extract of *D. viscosa* showed inhibitory effects against some pathogenic bacteria and *Candida albicans*. Ethanolic and diethyl ether extracts of leaves and bark established maximum inhibitory effect against test pathogenic bacteria, maximum efficacy was recorded against *C. albicans* for the ethanolic extract of the bark (Esmaeel and Al-Jobori, 2011).

D. viscosa hot aqueous and methanolic extracts were examined for antibacterial effect against bacterial strains. *D. viscosa* hot aqueous extract indicated antibacterial activity against tested bacterial strains (MIC 7.3–16 mm) whereas, *D. viscosa* methanol extract revealed antibacterial profile against all tested bacteria (MIC 10–15 mm). Methanolic extract showed the highest antimicrobial effect against selected bacteria (Mothana et al., 2010). Extract of *D. viscosa* was used against selected bacterial strains from 16 µg/ml to 250 µg/ml showed the MIC of against *Escherichia coli* and *Enterococcus faecalis* (Teffo et al., 2010; Patel et al., 2013).

The hexane leaves extract of *D. viscosa* showed moderate activity against different bacterial strains (Nasrullah et al., 2012). Ethanol, methanol, and chloroform crude extracts of aerial parts of *D. viscosa* was examined for antibacterial and antifungal potential. Methanol and ethanol extracts indicated better results against the selected bacteria (Mehmood et al., 2013; Ramamurthy et al., 2013).

Different extracts of the whole plant of *D. viscosa* were screened for antibacterial profile using agar well diffusion technique against selected bacteria. The methanol 80% and chloroform 20% extract showed maximum inhibition zone against the tested pathogens (Jeya et al., 2014). Ethanol, petroleum ether and distilled water extract of *D. viscosa* were studied for antibacterial profile using agar well diffusion method (Orpin et al., 2018). The ethanolic extract at 4000 (µ/ml) showed the highest zone of inhibition (ZI) (11.67 mm) and lowest ZI (7.33 mm). *S. typhi* showed the result against ethanolic extract (11.67 mm), aqueous extract and petroleum ether.

The minimum inhibitory concentration (MIC) of triclosan (TRN), *D. viscosa* (PLE) and chlorhexidine gluconate (CHX) to inhibit *Candida albicans* strain was used by *in vitro*. 41 strains were used of *C. albicans*. A microtiter double dilution technique was used to measure the MICs of an acetone extract of TRN, PLE, and CHX, and 99.5% of the strains to kill. The MICs of TRN, CHX, and PLE were 0.0022–0.009, 0.008–0.16 and 6.25–25 mg/ml, respectively (Patel and Coogan, 2008).

The growth of *Aspergillus flavus*, *A. niger*, *Trichophyton rubrum*, *Paecilomyces varioti* and *Microsporum gypseum* were inhibited by chloroform, ethanol, aqueous, and ethyl acetate (EtOAc), methanol extracts of leaves,

stem, and fruits of *D. viscosa* (Pirzada et al., 2010). The fractions from the hydroalcoholic, aqueous, and n-hexane leaves extract of *D. viscosa* were evaluated against *Candida albicans* (62.5 µg/ml) (Khurram et al., 2011).

D. viscosa different solvent extracts of the leaves were studied anti-carcinogenic, anti-*S. mutants* and antibiofilm properties. The DVA flavone containing nanoparticles indicated anti-carcinogenic activity with improved substantively (Sebelemetja et al., 2020).

13.3.3 Antiulcer Activity

D. viscosa was used against ulcer. Antiulcer activity was determined by using different methods. The antiulcer activity of the extracts may be attributed to cytoprotective and healing activity (Veerapur, 2004). Gastric ulcer was induced by using ethanol and indomethacin in Wister rats. Water and ethanol extracts showed reasonable as juxtaposed to hexane extract. Hexane extract of *D. viscosa* showed significant results against ulcer activity, 90% protection at 500 mg/kg and gastric lesions induce by indomethacin, producing 92% protection at 500 mg/kg, (Arun and Asha, 2008).

13.3.4 Antidiabetic Activity

Different extracts of *D. viscosa* were used against diabetes. *D. viscosa* effects were estimated glucose homeostasis (*in vitro* studies). 66% coconut oil (1.1% v/w) and fructose (66% w/w) mixed with normal pellet diet (NPD) and feed for 1.5 months to rats (Veerapur, 2010; Arulselvan et al., 2014; Uddin et al., 2018). *D. viscosa* leaves extract revealed antidiabetic effects via alloxan-induced diabetes in rabbits (Akhtar et al., 2011). The EtOAc and methanolic extract of *D. viscosa* leaves was determined the diabetic effect. Methanolic leaves extract of *D. viscosa* showed antidiabetic effect in diabetic rats (Jagra et al., 2011).

Crude extracts of *D. viscosa* were tested for antidiabetic study through glucose tolerance test and STZ-diabetic in rats. The percentage of glucose reduction by methanolic extracts was 43.81% (Meenu et al., 2011). Solvent extract *D. viscosa* was used for antidiabetic study. Different test likewise alloxan-induced diabetic and glucose tolerance test was applied in rats. Butanol, aqueous, and ethanol extracts showed the reduction in blood glucose values to normal. The percentage of glucose reduction by butanol extract was 48%. The root juice of *D. viscosa* is traditionally used for the treatment of diabetics (Muthukumran et al., 2011).

The glucose uptake by isolated rat using hemidiaphragm *in vitro* model revealed the insulin 15.45 ± 0.12 in mg/g/min and extract of *D. viscosa* (13.80 ± 0.1697) showed better results as compared to control group (5.34 ± 0.12). This study concluded that *D. viscosa* will be alternative used for the treatment of diabetes mellitus (DM) (Rani et al., 2012). Crude extract of *D. viscosa* was used for antidiabetic profile by cholesterol, triglycerides, urea, protein, creatinine, SGPT, SGOT, SGPT, and blood glucose. Extracts show minimum glucose levels to normal limit and increase triglycerides, protein, urea SGOT, SGPT, creatinine, and cholesterol (Rani et al., 2013).

13.3.5 Anti-Inflammatory Activity

The leaves hydroalcoholic extract of *D. viscosa* was investigated against inflammatory effect. Carrageenan injection was used to induce edema in paw. Leaves extract 300 mg/kg was given orally. Extract showed greatest result (Khalil et al., 2006). Extract of *D. viscosa* leaves were estimated anti-inflammatory profile by ear edema models. The extract of *D. viscosa* indicated 97.8% anti-inflammatory effect (Salinas-Sanchez et al., 2012). The methanolic extract of *D. viscosa* indicated highest results of anti-inflammatory effects (Nayeem et al., 2019; Shafek et al., 2015; Necchi et al., 2012).

13.3.6 Antinociceptive Activity

D. viscosa extract was used to study antinociceptive activity by exerting different methods viz. tail flick, writhing induced by glacial acetic acid and hot plate method in rats and mice. Extract showed significant antinociceptive activity (Joshi et al., 2006). Viscosine was isolated from *D. viscosa*. Two methods were used (hot plate method and acetic acid-induced writhing). Viscosine showed significant antinociceptive profile (Khan et al., 2014).

13.3.7 Anticancer Activity

Two new antiproliferative Oleanna-type triterpenoid saponins, dodoneasides 1 and 2 were separated from *D. viscosa* extracts. Compounds 1 and 2 indicated antiproliferative activity in the A2780 human ovarian cancer cell line through IC_{50} values of 0.79 and 0.70 μ M, correspondingly (Cao et al., 2009).

75 µg/ml leaves ethanolic extract of *D. viscosa* used against breast cancer cells MDA-MB231 and showed good results of MTT assay, apoptosis, and cell cycle arrest (Mossa and Al-Shawi, 2015). 80% ethanolic extract of *D. viscosa* was studied for cytotoxic effect. The extract (IC₅₀ of 19.4 µg/ml) showed strong cytotoxic activity as compared to cisplatin (IC₅₀ of 5.48 µg/ml) (Mothana et al., 2010 and Shafek et al., 2015).

13.3.8 Antidiarrheal

Root extracts of *Dodonea viscosa* showed promising results of anti-diarrhea. Castor oil was used to induce diarrhea in mice. The diarrhea was reduced in mice by using aqueous and alcohol extracts. Extracts also reduce the weight of stools (Rajamanickam et al., 2010). 80% methanolic extract of *D. viscosa* leaf were used to determine antidiarrheal effects by using castor oil-induced diarrhea, gastrointestinal transit and enteropooling model in Swiss albino mice. Leaf extracts of *D. viscosa* showed significant result against diarrhea (Abdela, 2019).

13.3.9 Antimalarial Activity

Around 80% aqueous Me OH leaves extract of *D. viscosa* var. *angustifolia* used against malaria (Melaku et al., 2017). Extracts of *D. viscosa* var. *angustifolia* of seeds was experienced against *Plasmodium berghei*. Mice used as experimental animal. Seed extract showed promising results (Mengiste et al., 2012). The root methanol extract of *D. angustifolia* indicated the greatest results of parasitemia (84.52%) (Deressa et al., 2010; Clarkson et al., 2004).

13.3.10 Antiherpes Activity

The ethanolic extract of the *D. viscosa* of aerial parts displayed against anti-herpes activity (Oliveira et al., 2012).

13.3.11 Wound Healing Activity

D. viscosa flavonoid fraction and ethanol extract was studied by *in vitro* wound healing activity. The flavonoid fraction of *D. viscosa* showed better results

as compared to ethanolic extract. Flavonoid fraction of *D. viscosa* showed significant anti-healing properties (Shanthi et al., 2015). The ethanolic leaves extract of *D. viscosa* was examined for wound healing profile. Rats used as model animal. Ethanolic leaves extract showed significant wound healing properties (Joshi et al., 2003). In the excision method, 10% extract-treated wounds were indicated to have increased rate of epithelization, and wound contraction. Further, the extract facilitated the healing process, evidenced by the increase in the breaking strength of the incision and dead space wounds. Ethanolic extract in the form of cream produced a good result in all wound models studied.

Pawar and Mahajan (2013) evaluated *D. viscosa* methanolic extract for wound healing in diabetic Wister albino rats. In resection wound model, the elevation in rate of capillary number, reepithelization, matrix density and wound contraction was detected. As compared to control the collagen values was noticed better. For the antiinflammatory profile cotton pellet granuloma method was used. The ethanolic extract of *D. viscosa* was used in the form of lotion. In diabetic wound healing, *D. viscosa* lotion indicated vital role.

13.3.12 Insecticidal Effects

The aqueous, chloroform, and methanol extracts of the root, stem, and leaves of *D. viscosa* was exposed larvicidal study by using *Artemia salina* larvae. The leaves extract showed significant results against *Artemia salina* larvae (Kannaian et al., 2012). The alcoholic leaves extract of *Dodonaea viscosa* was examined against wax worm *Galleria mellonella* (Mohammed and Nawar, 2020).

13.3.13 Antioxidant Effect

D. viscosa ethanolic extract concentration showed the foremost potent antioxidant activity with inhibition metallic element. 0.9 ± 0.15 using the DPPH radical scavenging method exhibited a high effective scavenging activity (Shafek et al., 2015; Mothana et al., 2010). The results revealed that the ether soluble fraction exhibited the best percent inhibition of the DPPH radical as compared to the opposite fractions. It showed 81.14 ± 1.38 behavior therapy of the DPPH radical at a degree of 60 $\mu\text{g ml}$ (Riaz et al., 2012). Aerial parts

of *D. viscosa* were used to determine antioxidant and anticholinesterase activities. Different compounds isolated from *D. viscosa* by using different methods for antioxidants (Akthar et al., 2016).

The leaves extract of *D. viscosa* was studied for antioxidant properties via using DPPH process. The hexane leaves extract showed significant antioxidant properties as juxtaposed to other solvents extract of *D. viscosa* (Al-Habsi and Hossain, 2018).

13.3.14 Antifertility Effect

D. viscosa leaves methanolic extracts showed antifertility profile in female rats. The extract reduced significantly ($P < 0.01$) the quantity of litters when given through oral route. Due to the antifertility effect, the plant, therefore, is contraceptive as well as significantly showed anti-implantation and early abortifacient effect (Ramya et al., 2011). The leaf extract of *D. viscosa* was examined for its antifertility profile in rats. *D. viscosa* leaf extracts treatment decrease the glycogen within the testis and liver. The leaf extracts cause toxic manifestations on male system (Kumar et al., 2013).

13.3.15 Anti-Schistosomal Activity

D. viscosa leaves extracts were tested for anti-parasitic profile against *Schistosoma mansoni* infected mice. The result showed that *D. viscosa* extracts significantly reduced the production of eggs out up in *S. mansoni* infected mice and reduces the liver granuloma size (Bawazir et al., 2020).

13.3.16 Hepatoprotective Activity

The *D. viscosa* leaves extracts were exerted against hepatoprotective and antihyperlipidemic via alloxan induced diabetics in rabbits. The different extracts (aqueous and methanolic) indicated hepatoprotective effects also antihyperlipidemic (Ahmad et al., 2012). *D. viscosa* whole plant methanolic extract was exerted to determine the hepatoprotective effects by using CCl_4 -induced hepatotoxicity in rats. *D. viscosa* extracts showed better results against hepatotoxicity (Ali et al., 2014).

KEYWORDS

- chlorhexidine gluconate
- *Dodonaea viscosa*
- herpes simplex virus type 1
- minimum inhibitory concentration
- normal pellet diet
- triclosan

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CHAPTER 14

Phytochemistry and Pharmacology of *Flueggea virosa* (Roxb. ex Willd.) Royle

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14.1 INTRODUCTION

Flueggea virosa (Roxb. ex Willd.) Royle (Syn.: *F. microcarpa* Blume, *Securinega virosa* (Roxb. ex Willd. Baill.) belongs to a dicot Angiospermic family Phyllanthaceae. Some taxonomists place it in the family Euphorbiaceae, also known as spurge family. It is an evergreen small tree or a shrub, commonly called Chinese white berry or white-berry bush with smooth, gray bark. Leaves obovate, obtuse, sub-orbicular, narrowly based, glaucous with raised nerves beneath; petiole slightly winged. Flowers greenish both male and female; fruit snow-white, globose, juicy; seeds, shiny, brown. Flowering time starts from October to January and fruiting time starts from December to march (Ajaib, 2012).

F. virosa is used to cure health related problems (Kirtikar and Basu, 1975). The fruit is edible at maturity and pulp of fruit is used to cure itching by rubbing on the skin. The fruit is used against snakebites by chewing it. Leaf decoction is given to nursing mothers to cure lactation problems, sick babies at birth in Tanzania and Burundi. In Tanzania, leaf and root

decoctions are used to cure abdominal pain. In Yorubas of Southwestern Nigeria, leaf decoction is also use to treatment of fever (Yerima et al., 2009). In Northern Nigeria, mental diseases are also cured by using decoction of this plant (Okunola et al., 2018; Renu et al., 2018) reviewed phytochemistry and pharmacology of *Securinega virosa*.

14.2 PHYTOCHEMISTRY

The phytochemical screening of *F. virosa* revealed the occurrence of triterpenoids (Monkodkaew et al., 2009), tannins (Ezeonwumelu et al., 2012), alkaloids (Freiburghaus et al., 1996), flavonoids, and saponins (Magaji et al., 2008) resins, steroids (Tanko et al., 2008), cardiac glycosides and anthraquinones (Magaji et al., 2007), *ent*-phyllanthidine, virosecurinine, quercetin, kaempferol, 11-*O*-acetyl bergenin, kaempferol, virosecurinine, daucosterol, quercetin, and β -sitosterol (Wang et al., 2008). Bark and leaves of *F. virosa* indicate the presence of flavonoids, reducing sugars, glycosides, saponins, and terpenoids (Ajaib, 2012; Ajaib et al., 2018). There are five groups of alkaloids, i.e., Securine type alkaloids (Virosecurinine, viroallosecurinine (root bark) (Saito et al., 1964) and flueggeidine; Neosecurine alkaloids (Virosine A and Virosine B (twigs and leaves); Norsecurinine-type alkaloids (Norsecurinine, dihydronorsecurinine (root bark) (Saito et al., 1964), 14, 15-dihydronorsecurinine (virosine), 14, 15-Epoxynorsecurinine (root bark) (Dehmlow et al., 1999), Flueggeainol, flueggeainol eather, Virosaine A, and Virosaine B, Neonorsecurinane alkaloids (Bubbialine and bubbialidine); Norsecurinine-derived oligomeric alkaloids (twig and leaves) (Zhao et al., 2011), alkaloid dimmers norsecurinamines A and B derived from (fruit) (Wang et al., 2016), flueggenine A, flueggenine B (root) (Gan et al., 2006), flueggenine C, flueggenine D, fluevirosine A, fluevirosine D, and fluevirosinine A (Knolker, 2015). Flueggethers B and C are dimmers, while Flueggether D are trimer. Twigs and leaves are a big source of three securing alkaloids (Zhang et al., 2016). Root bark is a source of bergenin (Magaji et al., 2015). Young branches with leaves of the plant are a source of Friedelin, epifriedelanol, stigmasterol, and betulinic acids (Monkodkaew et al., 2009). Leaves contain gallic acid, ellagic acid, rutin flavonoides and isocoumarine bergenin flavonoids quercetin. The bark of a stem has friedelinol and triterpenes friedelin. Dried root extract in aqueous gives tannins, cardiac glycosides, saponins, and steroids. The twigs have 8% tannins. Bark of root has 0.4–0.6% alkaloids. The intact root has 0.04% alkaloids (Dickson et al., 2006). *F. virosa* contain flueggenines A and B in fruit and roots (Liu et al., 2005), 4E-dehydrochebulic acid, 1. Abeo-*ent*-podocarpa-6,

8, 11, 13-tetraene, 2. Trimethyl ester, 3. Pentaen-3-one, 4. Ent-podocarpanes, 5. Ent-podocarpanes, 6. 3, 4,-Seco-30-nor-friedelanes (Figure 14.1). 1. Norsecurinic Acid, 2. Flueggenines A, 3. Flueggenines B (Figure 14.2). 1. 15b-butoxy-14, 15-dihydronorsecurinine, 2. 15a-14, 15-dihydronorsecurinine. Bergenin, 2. Menisdaurin, 3. Amiroside, 4. Ent-phyllanthidine, 5. Securinine, 6. Securinol, 7. Virallo Securinine (Figure 14.3).

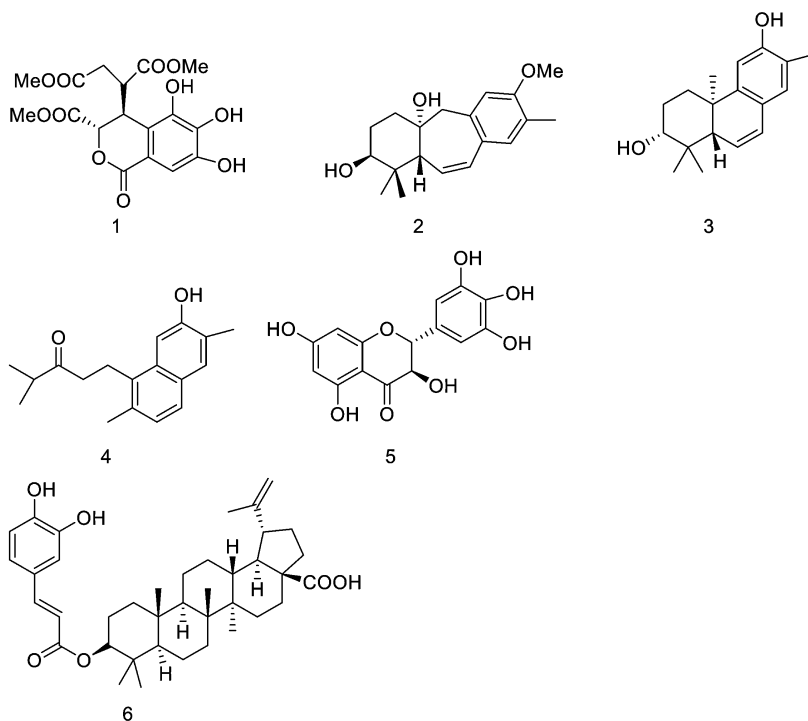


FIGURE 14.1 1. Trimethyle ester, 2. Abeo-ent-podocarpa-6, 8, 11, 13-tetraene, 3. 3beta, 12-dihydroxy-13-methylpodocarpa-6,8,11, 13,-tetraene, 4. 12-hydroxy-20(10-5)-abeo-4, 5-seco-podocarpa-5(10), 6. 8,11, 13- Pentaen-3-one, 5. (+) ampelosin E., 6. Butulinic acid 3beta-calfeate, (Chao et al., 2016)

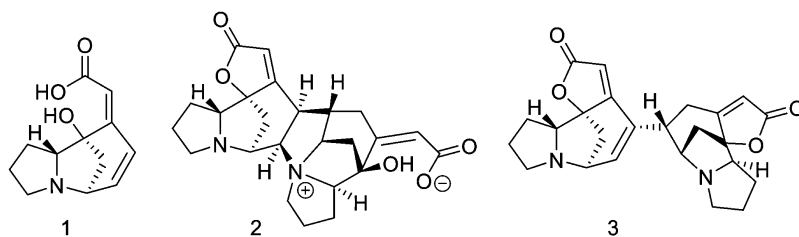


FIGURE 14.2 (1) Norsecurinic acid (Chen and Hou, 1985; Dehmlow et al., 1999); (2) flueggenines A; (3) flueggenines B (Gan et al., 2006).

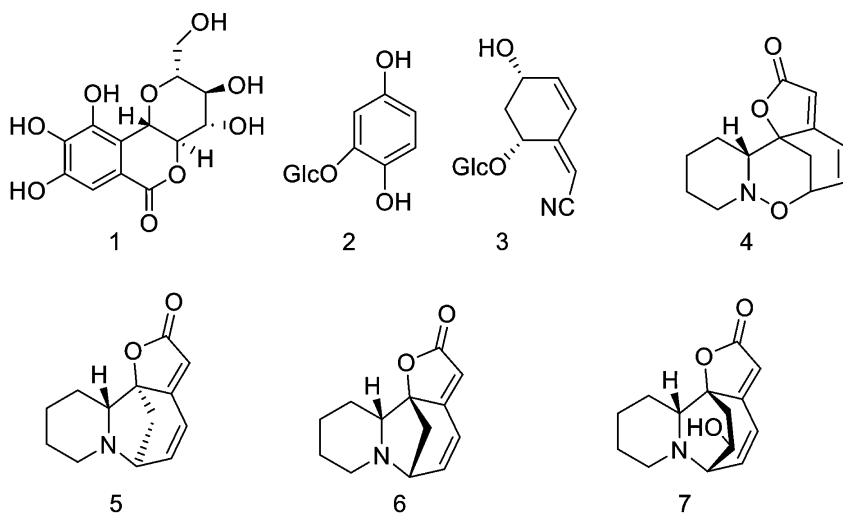


FIGURE 14.3 (1) Bergenin; (2) menisdaurin; (3) amiroside; (4) ent-phyllanthidine; (5) securinine; (6) securinol; (7) virallo securinine.

14.3 PHARMACOLOGY

F. virosa is sometimes placed in family Euphorbiaceae, and almost all species of Euphorbiaceae have properties of analgesics, wound healing abilities, and hemostatic anti-inflammatory (Udauk and Kola, 2010). Members of genus *Flueggea* have properties of painkiller and antiproliferation.

14.3.1 Antiviral Activity

Roots of *F. virosa* possess potential against anti-hepatitis C virus (HCV) as potent dinorditerpenes isolated by Chao et al. (2014). It was revealed from the results that compounds 1, 11, and 12 revealed potential anti-HCV activity at EC_{50} values of 5.6, 7.5, and 6.6 μ M, respectively. Chao et al. (2016) reported the almost similar results against anti-HCV using isolated terpenoids from *F. virosa*.

Zhang et al. (2015) isolated two new alkaloids, i.e., flueggether, and virosinine, from *F. virosa* and reported that both alkaloids showed mild anti-HIV activity. Root extracts also contain nonalkaloid dinorditerpenoides potent compounds against anti-HCV (Chao et al., 2014a, 2016). Trinorditerpenes that are flueggrenes isolated from the roots of plant was aggressive against anti-HCV (Chao et al., 2013).

14.3.2 Antimicrobial and Antifungal Activity

Antibacterial effects of ethyl acetate (EtOAc), ethanolic, and n-hexane extracts of *F. virosa* leaves was evaluated using agar well diffusion method against *Staphylococcus aureus* and *Klebsiella pneumoniae* and found significant results for EtOAc and ethanolic extracts whereas n-hexane did not show any result (Danlami et al., 2015). Root and bark of *F. virosa* using chloroform, petroleum spirit, ethanol extracts were tested against *Bacillus subtilis*, *Micrococcus flavus*, *Streptococcus faecalis*, *Salmonella abony*, *Staphylococcus aureus*, *E. coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Saccharomyces cerevisiae*, *Trichophyton interdigitale*, *Klebsiella aerogenes* and *Microsporum floccosum* (Dickson et al., 2006). The chloroform extract was the most active extract showing activity against 13 test organisms including some dermatophytes with 15.6 ug/ml, to 1000 ug/ml MIC values. The highest diameter of zone of inhibition (ZI) (22 mm) observed for the agar well diffusion method, was given by this extract against *M. flavus*.

Dried fruit pulp of 0.03% methanolic extract inhibited the growth of *Trichophyton mentagrophytes* (Tabuti, 2007; Sawhney et al., 1978). Leaf extracts were reported to inhibit the growth of *Yersinia pestis* (Collier and Van De Piji, 1949).

14.3.3 Analgesic and Anti-Inflammatory Activity

The methanolic extract of root bark and leaves have better analgesic and anti-inflammatory activity on animal models (Magaji et al., 2008; Yerima et al., 2009). In another study, the aqueous extract of dried root showed acute toxicity, analgesic, and anti-pyretic activity in Wistar rats (Ezeonwumelu et al., 2013).

14.3.4 Antidiabetic Activity

Tanko et al. (2008) concluded that after 24 h of methanol extract of *F. virosa* significantly decrease blood glucose levels in diabetic induced rats. Moshi et al. (2000) investigated that *F. virosa* distilled water extract lowered the area under the OGTT curve dose-dependently at doses between 0.1 and 1.0 g/kg body weight.

14.3.5 Sedative, Behavioral Effects, and Sleep-Inducing Activity

Bergenin isolated from root has shown sleep inducing properties (Magaji et al., 2015). The methanol leaf extract shows the appearance of carbohydrates tannins, saponins, alkaloids, flavonoids, resins cyanogenic glycosides and steroids. The saponins and flavonoids both are responsible for sedative activity in mice (Aiyelero et al., 2012).

14.3.6 Cardiovascular Protection

Various studies revealed that bergenin effectively enhanced arrhythmias induced by ligation of the coronary artery. Atrial fibrillation enhanced using 0.8 mg/kg bergenin in rabbits from 1.34 mV to 1.92 mV (Paris et al., 1955; Pu et al., 2002).

14.3.7 Antimalarial Activity

Methanolic leaves extract shows strong antimalarial effects. In a dose dependent manner, it decreases the growth level of *Plasmodium falciparum* (Kaou et al., 2007; Muthaura et al., 2007). *P. falciparum* culture of W2 and D6 were used to determine antimalarial activity. The culture media consisted of RPMI 1640 supplemented which have 10% serum. *Fluggea virosa* is an antimalarial and most active plant. Orally its decoction is used in morning and evening. It is also used for body bath from 3 days to one week. Most of the extract is obtain from *Fluggea virosa* that is so interesting. Evaluation of antimalarial activity was narrated for this plant from Cambodia and Zimbabwe, but there was no activity (Kraft et al., 2003; Hout et al., 2006). Clarkson et al. (2004) reported that bergenin showed a dose-dependent *in vitro* antiplasmodial activity.

14.3.8 Antidiarrheal Activity

Leaves, bark, root, stem, and bark of methanolic extracts of *F. virosa* on an animal model by using castor oil to induce diarrhea. It was observed in a model that the leaves and root bark have capabilities to study the effects of chemical compounds on living organisms, specially treatment of diarrhea (Magaji et al., 2007).

14.3.9 Anticancer Activity

Friedelin, epifriedelanol, stigmasterol, heptanolide, and betulinic acid are found in *F. virosa*. Betulinic acid is a great source of cytotoxic activity. In tumor cell lines, alcoholic extract of leaves have a major effect on cytotoxicity *in vitro*. Virosecurinine showed cytotoxicity. Foliage extracts revealed anticancer effect against cell lines of L1210 and P388 (Tatematsu et al., 1991). Viroalloscurinine was responsible for cytotoxicity in one of the cell lines (Tatematsu et al., 1991). The twigs and leaves showed Flueggine A and Flueggine B. These are two dimeric indolizidine alkaloids. Flueggine B decreases growth against Michigan Cancer Foundation-7 and MDA-MB-231 and MB (which stands for metastasis cancer of Breast) in human (Monkodkaew et al., 2009).

F. virosa contain flueggenines A and B in fruit and roots while only flueggene A possesses weak activity against the murine leukemia P-388 cells whereas flueggene B was found to be quiescent (Liu et al., 2005).

Monkodkaew et al. (2009) reported the anticancerous effect of the five triterpenes that were isolated from *F. virosa*. Their result showed that betulinic acid displayed good cytotoxicity against the cancer cell lines in humans.

14.3.10 Antioxidant Activity

F. virosa acetone extracts possess antioxidant activity with an IC_{50} value at 30 $\mu\text{g/mL}$, nearly approaching the ascorbic acid with an IC_{50} value of 25 $\mu\text{g/mL}$ may be due presence bergenin a potent antioxidant compound having an IC_{50} value of 921 μM (Chauke et al., 2012; Nyasse et al., 2004; Takahashi et al., 2003). Leaf extract of *F. virosa* had the highest phenolic content (156 mg GAE/g extract) and high phenolic content had a high antioxidant effect (Chauke et al., 2012).

Antioxidant and DPPH free radical scavenging effects using spectrophotometric and TBA lipid peroxidation assays were evaluated by Dickson et al. (2006). Chloroform extract showed IC_{50} DPPH value of 26.17 and IC_{50} TBA value of 45.76 $\mu\text{g/mL}$ (Danlami et al., 2013; Sanogo et al. (2009).

14.3.11 Antispasmodic Activity

Distilled water and ethanolic extracts of leaves, bark, and fruit showed antispasmodic activity against acetylcholine and histamine induced spasms and increased phenobarbitone sleeping time (Bhakuni et al., 1969).

14.3.12 Anti-Sleeping Sickness Activity

Antitrypanosomal activity of the extract of *F. virosa* was reported by Freiburghaus et al. (1996). The inhibitory activity of bergenin isolated from methanolic leaf extraction of *F. virosa*, on the growth of *Trypanosoma brucei* bloodstream form was established as well as its effects on three glycolytic enzymes of *T. brucei* (GAPDH, PFK, and PGK) by Nyasse et al. (2004). In fact, bergenin exhibited an inhibitory activity on the growth of the bloodstream form of *T. brucei* with an IC_{50} value of 1 mM when suramin (IC_{50} 0.22 mM) was used as the reference drug. Under the experimental conditions used, bergenin was considered as a moderate trypanocidal compound since its IC_{50} value was never below 0.5 mM. The bloodstream form of *Trypanosoma brucei* grows with an IC_{50} value of 1 μ M is inhibited by berginin (Tabuti, 2007).

14.3.13 Anthelmintic Activity

The effective anthelmintic potential was reported by Ajaib et al. (2018) at 100 mg/mL concentration of distilled water extract of *F. virosa*. The time for paralysis ranged from 11–29 minutes at a concentration of 100 mg/mL.

14.3.14 Activity Against Epilepsy and Convulsions

Among 11 Malian medicinal plants, ethanolic extracts of *F. virosa* being the most potent in both *in vitro* and *in vivo* antiepileptic activity and affinity to the benzo-diazepine binding site on the $GABA_A$ receptor in mice (Pedersen et al., 2009).

14.3.15 Antipsychotic Potential

Methanol leaf extracts of *F. virosa* at 100 mg/kg showed antipsychotic potential using apomorphine-induced stereotypic climbing behavior and swim-induced grooming tests in mice. It was revealed from the results that the high doses of extract reduced the apomorphine (1 mg/kg)-induced stereotypic climbing behavior after 30 min as compared to haloperidol (Magaji et al., 2014).

KEYWORDS

- anti-hepatitis C virus
- Euphorbiaceae
- *Flueggea virosa*
- pharmacology
- photochemical
- phytochemistry
- *Streptococcus faecalis*

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CHAPTER 15

Biomolecules and Pharmacology of *Rotula aquatica* Lour.

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15.1 INTRODUCTION

Rotula aquatica is an acclaimed medicinal plant with a wide range of biological activities. *R. aquatica* is utilized by the traditional medicine system for antiurolithiatic activity. The plant is also observed to have antimicrobial (Joshi and Devi, 2017), analgesic, antipyretic (Gupta et al., 2011), antidiarrheal (Singh et al., 2012), antihelmintic (Lakshmi et al., 2012; Zade et al., 2013) and anti-inflammatory (Mengi and Bakshi, 2009) properties. A systematic search for useful bioactivities from medicinal plants is now considered to be a rational approach in the management of kidney stones (Khare, 2007).

The plant is a small much-branched shrub, 60–180 cm in height, with numerous short lateral arrested branchlets often rooting. Leaves small, alternate, or fascicled, entire, or obscurely toothed. Flowers small, few, on short lateral branchlets, between the leaves and purple in color. Fruit a drupe with four crustaceous one-seeded pyrenes red or orange in color.

It is widely distributed in India from Kumaoun to Assam and western to southern India in the sandy and rocky beds of streams and rivers, often were occasionally submerged in floods (Lakshmi et al., 2012). It is also distributed in Sri Lanka, China, tropical southeastern Asia, Africa, Brazil, and Latin America.

Common names of this plant are Pashnabhedah (Sanskrit), Pashanabhed (Hindi), Pashanabheda (Telugu), Pasanabhed (Kannada), Seppunerunji (Tamil) and Kallurvanchi (Malayalam).

15.2 PHYTOCHEMICAL CONSTITUENTS

Pharmacognostical and phytochemical evaluation of different parts of *R. aquatica* (leaf, stem, root, flower, and fruit) showed the presence of alkaloids, flavonoids, phenols, saponins, steroids, tannins, terpenoids, anthraquinones, anthocyanin, quinones, volatile oils, proteins, and carbohydrates (Vijayakumari et al., 2013). These studies of crude drugs play a very important role in identifying the purity and quality of the drug. The antioxidant properties of medicinal plants with phenolic compounds such as flavonoid, phenolic acids and tocopherols have been reported by various researchers (Krings and Berger, 2001; Ali et al., 2008).

Flavonoids are important secondary metabolites of plants, modulating lipid peroxidation involved in atherogenesis, thrombosis, and carcinogenesis. Phenolic compounds are well known as antioxidant and scavenging agents against free radicals associated with oxidative damage (Ferguson et al., 2006).

Saponin has the property of precipitating and coagulating red blood cells. Some of the characteristics of saponins include formation of foams in aqueous solutions, hemolytic activity, cholesterol-binding properties and bitterness (Sodipo et al., 2000; Okwu, 2004). Triterpenoids are a large class of natural isoprenoids present in higher plants, which exhibit a wide range of biological activities. Steroids (anabolic steroids) have been observed to promote nitrogen retention in osteoporosis and in animals with wasting illness (Flores-Sanchez et al., 2002).

The antioxidant activity of proanthocyanidins has been demonstrated to be 50 times greater than that of vitamin C and 20 times greater than vitamin E. It helps to protect the body from tissue damage, cancer, and improve blood circulation by strengthening the capillaries, arteries, and veins (Majo et al., 2008; Owolabi et al., 2010; Letelier et al., 2011).

Carbohydrate is reported to have numerous roles in living things, such as the storage and transport of energy (starch, glycogen), structural components (cellulose in plants, chitin in animals) and involve in process of the immune system, fertilization, pathogenesis, blood clotting and development (Madziga et al., 2010).

HPTLC analyzes confirm the presence of active compounds with bioactive properties. In HPTLC analysis of aqueous root extract of *R. aquatica* showed the presence of three different types of alkaloids, three different types of flavonoids, seven different types of phenols, 11 different types of saponins, steroid, tannin, and five different types of terpenoids (Vijayakumari et al., 2016, 2017).

From the GC-MS analysis, it was concluded that the aqueous root extract of *Rotula aquatica* contained hydrocarbon compounds with the carbonyl group and acid functional groups. The triterpenoid was isolated from the aqueous root extract of *Rotula aquatica* (Vijayakumari et al., 2016, 2017).

15.3 PHARMACOLOGY

15.3.1 Antioxidant Activity

The different parts of the plant (leaf, stem, and root) of *Rotula aquatica* exhibited various enzymatic (catalase (CAT), peroxidase, polyphenol oxidase, glutathione-S-transferase, and glutathione peroxidase) and non-enzymatic antioxidant (ascorbic acid, α -tocopherol, and total polyphenol) activities to support their utility (Vijayakumari et al., 2013).

15.3.2 Antidiabetic Activity

R. aquatica is found in antidiabetic drug formulations. An antidiabetic efficiency study was conducted on diabetic induced rats (Shyam et al., 2013). The plant extracts showed hypoglycemic activity by the reactivation of destructed pancreatic β -cells and potentiate them to secrete insulin (Ivvora et al., 1989). Antidiabetic activity of *R. aquatica* extract could be related to the presence of tannins and triterpenoids (Klein et al., 2007). Phytochemical screening of *Rotula aquatica* disclosed the existence of bioactive metabolites like triterpenoids and tannins (Vijayakumari et al., 2013). Hence, the antidiabetic activity of this plant is probably due to the presence of the above bioactive compounds and seems to have a promising value for the development of potent phytomedicine for diabetes (Mukesh et al., 2010).

15.3.3 Antiuro lithiatic Activity

Christina et al. (2002) have documented the antilithic activity of *R. aquatica* in male Wistar rats. *R. aquatica* at various concentrations possesses an inhibitory effect against crystal nucleation and aggregation. The components present in the aqueous root extract might be responsible for this preventive action against kidney stone formation (Vijayakumari et al., 2017). Calcium oxalate (CaOx) is the main constituent in the majority of kidney stones followed by calcium phosphate, struvite, uric acid (UA) and cysteine or drug-related stones. A reduction in oxalate was observed on plant extract treatment. This might be due to the inhibition of formation of oxalate by the plant extract (Hussain et al., 2012). There was a significant reduction in the contents of calcium, oxalate, and phosphate in aqueous root extract administered animals. Sequestering of this insoluble calcium salts by the fruit juice might be due to effective single or mixed ligand chelation by the hydroxyl acids present in them. The hydroxyl acids are expected to form metal ion complexes with calcium. The presence of hydroxyl acids in urine may decrease the amount of ionized calcium available for CaOx precipitate.

The urine protein, UA, and creatinine were significantly decreased plant extract treated groups. This might be attributed to the ability of triterpenes to reduce the level of oxalate supersaturation in the tissues, by way of their diuretic activity, which has been already documented (Anand et al., 1992). Crystal deposition in the kidney decreases Glomerular Filtration Rate (GFR). Due to the obstruction to the outflow of urine in the urinary system, waste products, particularly nitrogenous substances such as urea, creatinine, and UA get accumulated in blood (Tatiya et al., 2007).

15.4 MOLECULAR DOCKING

Molecular docking is an efficient technique to predict the predominant binding modes of the ligand with the protein of known three-dimensional structure. The active compound 3-O-Acetyl-11-Keto- β -Boswellic acid showed good interactions with Tamm-Horsfall protein (THP) having the least glide score of -2.35 (Vijayakumari et al., 2017).

THP is one of the main components of urinary protein origination from the kidney. The action of THP as an inhibitor or a promoter of CaOx crystal growth and aggregation appears to depend on the degree of its aggregation, ionic strength of the medium and the glycoprotein concentration. At low ionic strength, urine THP acts as an inhibitor of CaOx crystallization (Lopez et al.,

1986). The inhibitory action is also pronounced at very low concentrations of THP (Scur and Robertson, 1986). Moreover, THP becomes a promoter of CaOx aggregation due to a tendency to self-aggregation, which removes it from effective interaction with CaOx monohydrate crystals (Lopez et al., 1986).

KEYWORDS

- antidiarrheal
- calcium oxalate
- glomerular filtration rate
- phytochemical
- *Rotula aquatica*
- Tamm-Horsfall protein

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CHAPTER 16

Bioactives and Pharmacology of *Capparis decidua* (Forssk.) Edgew. (Syn.: *Capparis aphylla* Roth) (Family: Capparaceae)

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16.1 INTRODUCTION

Capparis decidua is a bush or small tree, branches are leafless at some periods of life cycle with pairs of straight and glabrous green spines, flowers are red/yellow and found on short lateral shoots, fruits are small, berry slightly beaked green that turn red on ripening. It occurs in mixed xeromorphic woodland and Psammophytic shrub vegetation, woody species of arid regions and desert parts of the Indian subcontinent, Saudi Arabia and Africa, vegetation cover in hot, sandy desert areas, potential to grow well on alkaline, sandy, and gravel soils and can thrive on shallow, hard soils, and rocky outcrops. Kair can be found at an altitude ranging from 300–1200 m with mean annual rainfall of 100–750 mm and mean annual temperature of 25–41°C. It grows well on soils with lower soil sodicity. The plant occurs

in North and Western Himalaya, sandy areas of Rajasthan, Haryana, Punjab, and salty ranges of Maharashtra, Karnataka, Andhra Pradesh, and Tamil Nadu. Vernacular names of the plant include Kair (Rajasthan), Karil (Uttar Pradesh), Ker (Gujarat), Teent (Haryana), Delha (Delhi, Punjab), Nepti (Western Maharashtra).

16.2 BIOACTIVES

Capparis decidua contains a number of alkaloids, terpenoids, glycosides, and fatty acids (Rathee et al., 2010a, b; Soda, 2010). One diterpene alcohol, two sterols, one diterpenic ester and two aliphatic constituents have been reported from *Capparis* root barks. Sitosterol has also been isolated from the roots with ethanol, neutral alumina separation in the presence of organic eluents benzene, chloroform, ether, and methanol successively. Empirically the two sterols are 24-b-methylcholest-7-ene-22-one-3b-ol and 24-b-methylcholest-9(11)-ene-22-one-3a-ol, whereas, one diterpene alcohol is 3-methyl-7-hydroxymethylene-10-(12,16,16-trimethylcyclohex-11-eneyl)-dec-9-ene-5-one-8-ol. The Butyl-3-oxoeicosanoate and 25-oxooctosan-1,20-diol are the two aliphatic constituents. One diterpene ester is identified as 9-(11,15,15-trimethylcyclohex-11-ene-13-one-yl)-one-6-hydroxymethylene-7-one-yl,4'-Meeptanoate (Nazar et al., 2020; Rathee et al., 2010a). Extracts isolated from chromatographic separation from the aerial parts concluded the presence of one shikimate derivative, four fatty acids, two acyclic terpenoids, two turpins and two sterols terpenoids (Singh and Singh, 2011). Two sesquiterpene lactones, germacr-3b-ol-12-ene-6,14-olide-15-oic acid and germacr-3b-ol-7,9-dien-6,14-olide-15-oic acid have been isolated and identified from methanolic extracts of aerial parts (Mohammed et al., 2014).

Polyamines spermidine and spermine have shown antioxidant, anti-allergenic, and anti-arteriosclerotic properties. They are important for growth, proliferation, development of mammalian cells and help in healthy hair growth (Soda, 2010; de la Pena et al., 2014; Ramot, 2011). Isocodonocarpine (Rathee et al., 2010a), capparidisine (Ahmad et al., 1992) and capparisinine (Ahmad et al., 1987; Dahot, 1993) are the important spermidine alkaloids separated and identified from *C. decidua* root bark. Other alkaloids such as, 14-N-acetyl isocodonocarpine, 15-N-acetyl capparisine, cadabicine (Ahmad et al., 1989, 1992), capparisine (Gaind and Juneja, 1970), codonocarpine (Ahmad et al., 1992) and stachydrine, (Gaind et al., 1969) have also been separated and purified from root bark. The chemical structures of some of the alkaloids present in the *C. decidua* are presented in Figure 16.1 (Dhankad et al., 2016).

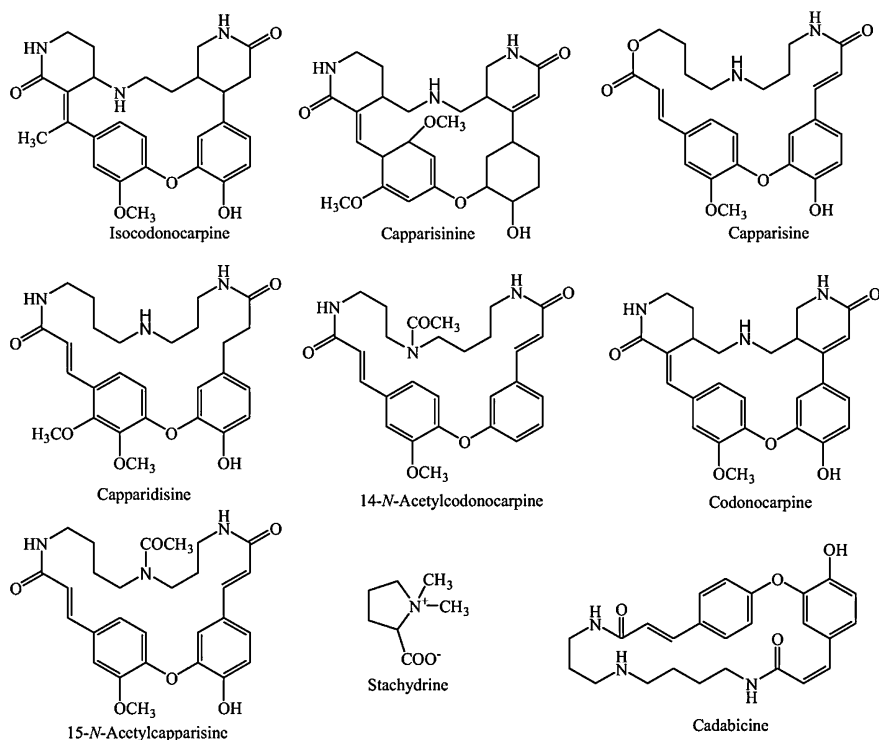


FIGURE 16.1 Chemical structures of some of the alkaloids present in the *C. decidua* (Reprinted with permission from Dhakad et al., 2016. <https://creativecommons.org/licenses/by/4.0/>)

Water-soluble 1-stachydrine (2-carboxy-1,1-dimethyl pyrrolidine) alkaloid has been isolated from the flowers, fruit husk, fruit pulp and root bark (Ahmad et al., 1985, 1987, 1989). Unsaponifiable fraction of seeds and fruit husk contain sitosterol, n-pentacosane, and large quantity of carotene (210 mg kg^{-1}) (Mishra et al., 2007) as well as phthalic acid (Dahot, 1993). In the leaves, aqueous n-hexane and acetone extracts of *C. decidua*, phenolic compounds, isorhamnetin, flavonoids, and flavonols were reported (Mann et al., 2013; Baghiani et al., 2012).

Leaves were observed with phenolic constituents like salicylic acid, vanillic acid, protocatechuic acid, phydroxybenzoic acid, syringic acid, gentisic acid, 2-hydroxy-6-methoxybenzoic acid and sinapic acid (Abra and Ali, 2011; Mann et al., 2013; Baghiani et al., 2012). Phenolic compounds, flavonoids, and flavonols from the leaves extracts and other phytochemicals have been isolated from various parts of *C. decidua* (Dahiya et al., 2019; Nazar et al., 2020) are shown in Table 16.1. The structures of some

important acidic phytochemicals from *C. decidua* are also described by Nazar et al., 2020.

Extracts isolated from different parts of *C. decidua* concluded presence of phytochemicals like alkaloids derivative from root (Singh et al., 2011), heterocyclic compounds (Gupta and Ali, 1997); sitosterols (Rathee et al., 2010a) and alkaloids (Rathee et al., 2010a) from root bark, terpenoids (Gupta and Ali, 1997); sesquiterpene lactones (Mohammad et al., 2014) from aerial parts, flavonoids and phenolic components (Baghiani et al., 2012; Abra and Ali, 2011) from leaves, stachydrine (Ahmad et al., 1987); carotene (Mishra et al., 2007) from fruits, stachydrine (Ahmad et al., 1987), hydrocarbons (Mishra et al., 2007; Rathee et al., 2010a,b), sterols and sugars (Rai, 1987) from flowers, glucocapparin and methyl isothiocyanate (Rathee et al., 2010a,b); *N*- pentacosane, β - sitosterol and β - carotene (Ahmad et al., 1987; 1992), and fatty acids (Abra and Ali, 2011) from seeds.

TABLE 16.1 Phenolic Compounds, Flavonoids, and Flavonols in the Leaves of *C. decidua*.

Extracts	Phenolic Compounds ($\mu\text{g mg}^{-1}$)	Flavonoids ($\mu\text{g mg}^{-1}$)	Flavonols ($\mu\text{g mg}^{-1}$)
Aqueous	154.0	98.30	148.30
<i>N</i> -hexane	357.0	812.30	868.30
Acetone	49.8	106.30	341.00

(Reprinted from Dahiya et al., 2019. <https://creativecommons.org/licenses/by/3.0/>)

Fruits are a rich source of protein (8.6%), vitamin C (7.8 mg/100 gm of pulp), sugar (immature fruit-1.7%, mature-3%) and potassium (3.23%) contents (Gupta et al., 1989; Vyas et al., 2009). Flowers contain hydrocarbons nonacosane and triacontane. In the flowers and fruit husk, oxalic acid (1 mg kg^{-1}), ascorbic acid (1190 mg kg^{-1}), phytic acid (680 mg kg^{-1}) and phthalic acid have also been detected (Rathee et al., 2010 a, b; Mishra et al., 2007). Two new saturated aliphatic ketones (C28 and C32), b-sitosterol, two free sugars, D glucose, D galactose, n-nonacosanol, b-D-glucoside of b-sitosterol, a new isomer of b-sitosterol, a new glycoside, pelargonidin-3-galactoside, glucocappasalin, and glucocapparin were found to be present in *C. decidua* flowers (Rai, 1987). The structures of some phytochemicals present in different parts of *C. decidua* are shown in Figure 16.2.

Spectral studies showed six oxygenated heterocyclic constituents that have been identified as; *Capparis* terpenoides (d-lactone derivatives of

1,3,3-trimethyl-1,4-cyclohexadien-6-one) from alcoholic extract of root bark and capparitis terpenolide (3-carboxy-6,17-dihydroxy-7,11,15,19-tetramethyleicos-13-ene-d-lactone) from flowers and fruit husk. The chemical composition of these six oxygenated heterocyclic constituents were given as 7, 11, 15, 19-tetramethyleicos-13-ene-17-ol-6,21-olide, 13-(15,19-trimethylcyclohex-14,17-diene-16-one-yl)-10-methyl-6-hydroxymethylene-tridec-10-ene-7,8,12-triol-5-(20)-olide, 13-(15,19-trimethylcyclohex-14,17-diene-16-one-yl)-10-methyl-6-hydroxymethylene-tridec-6-ene-1,8,12-triol-5-(20)-olide, 13-(16,20,20-trimethylcyclohex-15,18-diene-17-one-yl)-11-methylpentadec-1,22-dihydroxymethylene-7-ene-13-one-6,21-olide, 19-(21,25,25-trimethylcyclohex-20)30-diene-22-one-yl)-16-methyl-nonadec-8-ene-14-one-8-hydroxymethylene-18-ol-7,26-olide-28-oicacid, and 14-(16,20,20-trimethylcyclohex-15,18-diene-17-one-yl)-tetradec-3-ene-13-ol-1 (5), 8(24)-diolide, respectively (Gupta and Ali, 1997).

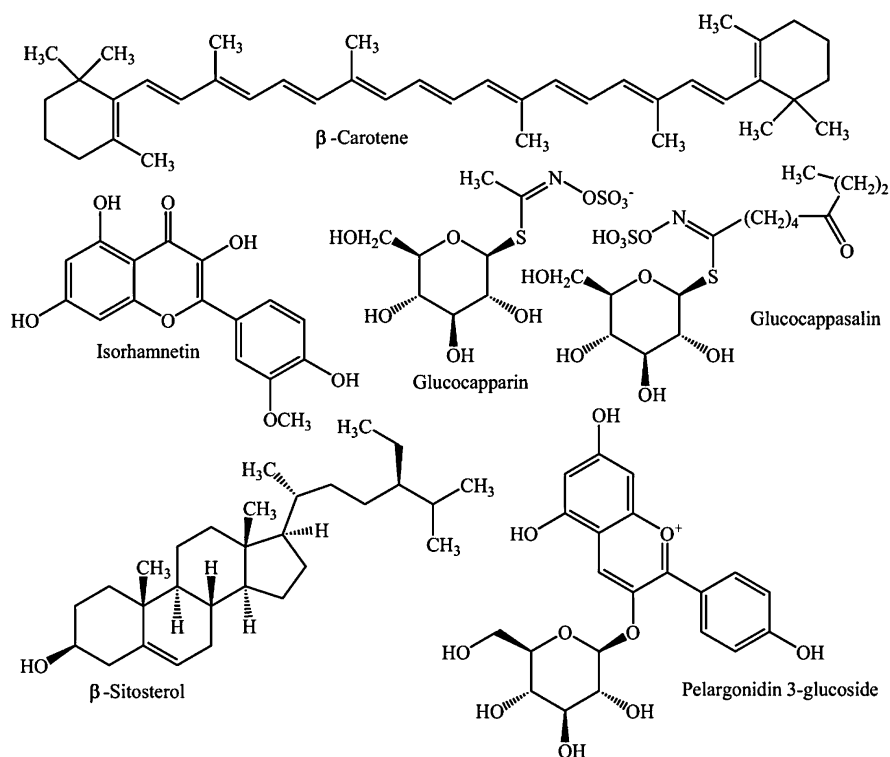


FIGURE 16.2 Structures of some phytochemicals present in different parts of *C. decidua* (Reprinted from Dahiya et al., 2019. <https://creativecommons.org/licenses/by/3.0/>)

Colorless, crystalline, and hygroscopic alkaloids capparine ($C_{15}H_{35}N_3O_6 \cdot 2H_2O$, MP 236°C), capparinine (MP 236°C) and cappariline ($C_{15}H_{35}N_3O_6 \cdot 5H_2O$, MP 188°C) were identified in roots and have isolated and used in pharmaceuticals (Rathee et al., 2010 a, b; Singh et al., 2011).

The seeds of *C. decidua* are rich source of high-quality oil (20%), of which 68.6% are unsaturated fatty acids and 31.4% are saturated fatty acids. Glucocapparin and a highly volatile antibacterial volatile compound methyl isothiocyanate which exhibit anticancer activity have been reported in the methanolic extracts of the seeds (Rathee et al., 2010 a, b; Tesoriere et al., 2007). In distinction to unsaponifiable fraction of seeds b-sitosterol, n-pentacosane, and b-carotene have also been separated and identified (Ahmad et al., 1987, 1992). Structural composition of isolated fatty acids from seeds of *C. decidua* were given by Nazar et al., 2020. Their research studies showed that in *Capparis* seeds, percentage fatty acids are as follows; Oleic acid (57.1%), Palmitic acid (21.1%), Linoleic acid (11.3%), Stearic acid (7.7%), Arachidic acid (2%) and Myristic acid (0.6%).

16.3 PHARMACOLOGY

16.3.1 Anticancer Properties

Glucosinolates are considered to be having anticancer properties (Mishra et al., 2007). Stachydrine isolated from *C. decidua* is a potent anti-metastatic agent, which can markedly restrict the malignancy and the invasive capacity of malignant cancer cells (Cheng et al., 2020). Stachydrine affects the invasion and metastasis of cancer cells by inhibiting the expression of chemokine receptors (CXCR3 and CXCR4) of prostate cancer (Rathee et al., 2012). Rathee et al. (2012) observed a dose dependent decrease in expression of mRNA and protein levels in stachydrine-treated human prostate cancer cells (PC-3 and LNCaP) which has been detected by reverse transcriptase-polymerase chain reaction (RT-PCR).

16.3.2 Hypocholesterolemic Activity

The extracts of unripe fruits and shoots of *Capparis* causes reduction in plasma triglycerides, total lipids, and phospholipids (Goyal and Grewal, 2003) and can be used as hypocholesterolemic syrup or hypolipidemic drug (Chahlia, 2009; Singh and Singh, 2011). Dietary fiber content of *C. decidua*

varied from 38.5–55.5%. A 10% of the diet supplements with hemicelluloses from *C. aphylla* to rats have found induced a greater resistance to hyperlipidemia than cellulose and has more pronounced hypocholesterolemic effect (Agarwal and Chauhan, 1988).

16.3.3 Anti-Fertility Activity

Capparis shoot with *Peganum harmala* shoot used as antifertility drug, stem, wood coal is used in muscular injuries and leaves used in alveoritis and pyorrhea. From herbal oral contraceptive mixture containing methanol extracts of aerial part of *Capparis aphylla* having anti-fertility activity, is known to be potent contraceptive activity in folklore Indian literature. Singh et al. (2018) used different doses like 200, 300 and 400 mg/kg of herbal oral contraceptive suspension (HOCS) to mice, and checked a significant weight reduction ($p < 0.05$) of reproductive organs like epididymis, testis, and seminal vesicle in these HOCS treated rats. In the epididymis, the sperm motility and sperm concentration decreased, while sperm abnormalities enhanced and also the duration of motility of sperms decreased with respect to variable doses of HOCS. Hence these results showed disruption of the spermatogenic as well as androgenic properties in *C. aphylla* (Rajan et al., 2013; Singh et al., 2018).

16.3.4 Anti-Platelets Properties

Capparis has antiplatelet activity. In the aerial parts of *Capparis decidua*, two new sesquiterpene lactones were isolated and identified such as, MW-6 (Germacr-3 β -ol-12-ene-6,14-olide-15-oic acid and Germacr-3 β -ol-7,9-dien-6,14-olide-15-oic acid) and these isolates have shown potent and effective antiplatelet activity tested by using of guinea-pig platelets rich plasma mode (Mohammed et al., 2014; Vaishnav et al., 2015).

16.3.5 Anti-Arthritis Activity

Capparis is used in rheumatic arthritis patients and has antirheumatic properties (Kamal et al., 2016; Sharma and Kumar, 2008). The pain-relieving potential of *Capparis spinosa* roots in rat models of osteoarthritis and rheumatoid arthritis were evaluated by Maresca et al. (2016). *C. spinosa* extracts which have spermidine alkaloids and stachydrine, after single administration, it relieved

pain caused by rheumatoid arthritis and osteoarthritis. In their trials, the different preparations of *C. spinosa* (3, 30, 100 and 300 mg/kg) were acutely administered p.o. Powdered roots (300 mg/kg), DEC (100 mg/kg), and EtH₂O (300 mg/kg) were proved effective to manage arthritis. In both the treated model rats, hypersensitivity was significantly reduced to mechanical noxious stimuli as well as spontaneous pain treated as hind limb bearing alterations. The flower and fruit of *C. deciduas*, soaked in water and juice, is used for the treatment of rheumatism (Kamal et al., 2016; Sharma and Kumar, 2008).

16.3.6 Antioxidant and Anti-Aging Properties

C. decidua has antioxidant properties (Dangi and Mishra, 2011; Haq et al., 2011). The antiaging effect has also been seen with this plant (Jadoon et al., 2015). In the flower buds of *C. spinosa*, polyphenol compounds as flavonols, hydroxycinnamic acids, flavan-3-ols were identified by Wojdylo et al. (2019). They worked on antioxidant properties (ABTS+, FRAP, and ORAC), butyrylcholinesterase (BuChE) of the buds and antiaging activity (acetylcholinesterase (AChE)). They observed that total phenolic compounds depended on a genotype as well as growing stage of *Capparis* flowers and varied from 10,720 to 3256 mg/100 g dry weight (DW). In the flowers, the flavonols contained a mixture of different glycosylated such as quercetin (38–67%), myricetin (15–36%), kaempferol (4–7%) and isorhamnetin derivatives (0.8–3%) of total flavonols. In flavonols, ‘Nonpareilles’ and ‘surfines’ were higher than ‘fines’ and ‘gruesas.’ ‘Nonpareilles’ accumulated the more amounts of bioactive compounds that directly correlated with antioxidant, and antiaging properties, and were more potent BuChE than AChE inhibitors (Wojdylo et al., 2019).

16.3.7 Hepatoprotective Activity

By administration of CCl₄, the hepatotoxicity produced in paraffin oil (1:9 v/v) at treatment @ of 0.2 ml/kg for 10 days was measured to be inhibited by simultaneous oral administration of aqueous and methanolic extracts of *C. decidua* aerial parts; stem (200, 400 mg/kg BW) for 10 days, with appraisal of decreased level of serum AST, ALT, ALP, and bilirubin (Ali et al., 2009, 2011).

Rehman et al. (2017) investigated the hepatoprotective effects of aqueous-ethanolic extract of *C. decidua* (stems) against paracetamol (PCM)-induced liver injury in test animals. The level of improvement, biochemical parameters such

as SGOT, SGPT, ALP, and total bilirubin levels, along with histopathological changes in liver tissues were thoroughly analyzed. Reference drug used was Silymarin (50 mg/kg, p.o.). In these trials, the biochemical parameters levels were increased in rabbits that were intoxicated by PCM. Rabbit treated with *C. decidua* extract @750 mg/kg, BW, observed with maximum reduction of biochemical parameters in a significant manner. The hepatoprotective activity was also confirmed by histopathological examination of the liver tissues of control and treated groups. The presence of alkaloids, tannins, saponins, and flavonoids were also revealed by the phytochemical screening of the extracts. Therefore, the observations and data of the studies suggested that the different doses of *C. decidua* possess significant hepatoprotective effect, and this effect might be due to the presence of tannins and flavonoids.

16.3.8 Antibacterial, Antifungal, and Antiviral Activity

Capparis is esteemed for its antibacterial properties (Gull et al., 2015; Keymanesh et al., 2009; Sharma and Kumar, 2008). The organic solvent extract of fruit and stem of *C. decidua* was observed with excellent antibacterial activity against tested bacteria viz. two-gram positive bacteria, i.e., *Bacillus subtilis* and *Staphylococcus aureus* and two-gram negative bacteria, i.e., *Pseudomonas aeruginosa* and *Escherichia coli*. The crude ethanolic extract of stem showed the antibacterial activity maximum against *Pseudomonas aeruginosa* (~21.33) and showed comparative less antibacterial activity against *Escherichia coli* (~4.67). The chloroform and ethanolic extracts of *C. decidua* were observed with significant zones of inhibition for all microorganisms (Ishtiaq et al., 2017). Seeds are reported to have antibacterial activity due to isothiocyanate aglycon. The glucocapparin being deficient in antibiological properties, its derivatives isothiocyanate aglycon exhibits good antibacterial activity. It was shown inhibitory to cell cultures of *Vibrio cholerae* (Juneja et al., 1970).

16.3.9 Skin Diseases

The seed oil is rich in nitrogen and sulfur and can be used to cure skin diseases. From *C. decidua* nociceptive activities are also attributed to its various plant parts (Dev et al., 2015). Sharma et al. (2011) have observed that *C. decidua* has antidermatophytic potential, which was analyzed and experimentally generated dermatophytic lesion was topically treated in rats. *Trichophyton mentagrophytes* was inoculated into rats, and then these

infected rats were topically treated with 5 mg/g terbinafine and 5, 10 mg/g of experimental extract ointment. Dermal infection was completely recovered on 16th day of treatment by test extract ointment as compared to reference drug terbinafine which gave complete recovery on 12th day of treatment. The test extract ointment proved better ointment for cure of dermatophytosis in rats without any disease recurrence incidences.

16.3.10 Constipation and Excretion

The extracts of *Capparis* increase fecal excretion of cholesterol as well as bile acids (Agarwal and Chauhan, 1988). They observed dietary fiber content of 6 foods along with teent (*Capparis decidua*) varied from 38.5–55.7%. *Capparis* has hemicellulose fiber, fed at the 10% dietary level to mice. As a result, it induced more resistance to hyperlipidemia than cellulose. *Capparis* had good hypocholesterolemic potential which appears to operate through increased fecal excretion of cholesterol as well as bile acids. In the *Capparis*, dietary hemicellulose was observed with a negative correlation with liver cholesterol and serum and a significant positive relation with fecal bile acids. It was concluded by their studies that dietary fiber influenced total cholesterol, lipids, triglycerides, and phospholipids of the liver to varying extents.

16.3.11 Hypoglycemic Activity

Capparis is used in diabetes (Haq et al., 2011). Rathee et al. (2010b) explored antidiabetic activity of ethanolic and aqueous extract of *C. decidua* stem which were orally administered doses @ 250 and 500 mg/kg regularly for 21 days, to alloxan-induced (150 mg/kg, intraperitoneally) diabetic rats. After 21 days, results showed that aqueous and ethanolic extracts of stem have significant hypoglycemic and antidiabetic potential which decreased the fasting blood glucose level by 60.2, 98.51% (ethanolic extract) and 58.5, 83.6% (aqueous extract), with a different doses @ 250 mg and 500 mg/kg body weight, respectively.

Capparis fruits having hypoglycemic activity also alters free radical scavenging enzymes such as superoxide dismutase (SOD), reduces lipid peroxidation and catalase (CAT) in erythrocytes, kidney, liver, and in heart in aged alloxan-induced diabetic rats. The powder of fruits was applied against alloxan induced oxidative stress in diabetic rats and got the significant results to manage glucose levels (Yadav et al., 1997 a, b).

16.3.12 Heart-Rate Modulator and Antiatherosclerotic Property

Capparis has antiatherosclerotic activities (Purohit and Vyas, 2006). Capparisidine has dose-dependent depressant effect on heart rate and coronary flow. The maximum fall in coronary flow has been recorded at 1 mg/ml, the contraction and heart rate increased at a dose of 2 mg/ml. The dose dependent fall has been recorded up to 32 and 128 mg heart rate and in force of contraction, respectively (Rashid et al., 1989; Purohit and Vyas, 2006).

16.3.13 Anti-Inflammatory and Anti-Asthmatic Activity

Isocodonocarpine is found to be responsible for anti-inflammatory activity and anti-asthmatic effects. The ethanolic extracts of aerial parts exhibited both effects (Vaishnav et al., 2015).

KEYWORDS

- acetylcholinesterase
- butyrylcholinesterase
- *Capparis decidua*
- herbal oral contraceptive suspension
- paracetamol
- anti-inflammatory activity

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CHAPTER 17

Apium graveolens L. (Family: Apiaceae)

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17.1 INTRODUCTION

Apium graveolens L. belongs to the family Apiaceae. It is commonly known as Celery, Wild Celery. The vernacular names include Bari ajmod (Hindi), Bodiajamoda, Ajmud (Marathi), Bodiajamodia (Gujarati), Ugragandhika, Vastamoda, Hayagandha, Brahmakoshi (Sanskrit) and Jangali jwanu (Nepali). Celery is a biennial plant; leaves are pinnate to bipinnate with rhombic leaflets 3–6 cm long and 2–4 cm broad with creamy white flowers at a diameter of 2 to 3 mm obtained in the form of compound dense umbels. It contains ovoid to globose seeds with 2 mm long and wide (De Vilmorin and Roger, 1950). Initially, Celery was cultivated in Europe, especially in Italy, France as a food plant. Later on, the cultivation is continued in different countries like Algeria, Sweden, Egypt, Ethiopia, and Saudi Arabia.

Wet celery leaves intended to treat stomach and liver problems. Widely used for various menstrual problems and kidney stones. Traditionally it has been used to treat spasm and stomach problems in addition to diuretic, laxative, and sedative actions (Abdulrahman et al., 2017).

17.2 BIOACTIVES

Extensive investigation of *A. graveolens* for its various constituents responsible for potent biological activities was studied. As different parts of the plant are enriched with various bioactive molecules, all the different constituents were listed here. Methanolic fraction of the seed extract of *A. graveolens* (Celery) is loaded with flavonoids, alkaloids, carbohydrates, glycosides, and steroids (Khare, 2008). Majorly the plant contains phenols and furocoumarins like celerin, bergapten, apiumoside (Garg et al., 1979), apiumetin (Garg et al., 1978), apigravrin, osthenol, isopimpinellin, isoimperatorin, celereoside (Garg et al., 1980), 5 and 8-hydroxy methoxypsoralen, graveobioside A and B, apiin, apigenin, isoquercitrin, tannins, steroids, phenolic acids, terpenoids, flavonoids, volatile oils and saponins (Shad et al., 2011), phytic acid. Celery seeds, stems, and leaves enriched with volatile oils (Bos and Fischer, 1986), d-limonene-60 (Sipailiene et al., 2003), d-selinene, sedanonic acid and its anhydride and sedanolide (Chopra et al., 1992, 2009), sesquiterpene alcohols, fatty acids. The derived compounds were-selenine, limonene, β -eudesmol, β -pinene, camphene, cymene, α -thuyene, α -pinene, β -phellandrene, *p*-cymene, γ -terpinene, myristic, petroselinic, linoleic, palmitoleic, palmitic, oleic, myristoleic, stearic acid, santalol, α -eudesmol, sedanenolide, phthalide, and 3-n-butylphthalide. Celery tuber also contained methoxsalen (8-methoxypsoralen), 5-methoxypsoralen. Celery seeds contain 2 to 3% essential oil. Its oil contains mostly limonene, selinene, furanocoumarin and furanocoumaringlycosides and their flavonoids. Phytochemistry tests of celery seeds approve the presence of flavonoid apigenin (as main component), and vitamins A and C. The main components of the whole extract are limonene and myrcene (Al-Snafi, 2014). Celery leaves and stem contain phenols. Leaves contain luteolin, chrysoeriol 7-glucosides 48 mg/kg and 27 mg/kg, respectively. Celery leaves also contain furanocoumarin, bergapten, psoralen, xanthotoxin (Innocenti et al., 1976) and isopimpinellin (Taher et al., 2000). *p*-dimethyl styrene, *N*-p-tert-butyl benzene, caryophyllene, α -selinine, *N*-butyl phthalide (Bjeldanes and Kim, 1977), sedanenolide (Bjeldanes and Kim, 1978), sablone, β -elemene, trans-1, 2-epoxy limonene and thymol (Kooti et al., 2015). Seselin and apigravin, furanocoumarin glucoside, apimucoside, dehydrofurocoumarin glucoside, 2-dihydrofurocoumarins are present in the plant. Sesquiterpenoid glucosides (celeroside A–E), phthalide glycosides (celephthalide A–C) were isolated from the methanol extract of celery seed (Kitajima et al., 2003). Seeds husk contains graveobioside A and B, fatty acids, 7-octadecenoic acid. Essential oil constituents of root are buphthalide and neocnidillide (Fazal and Singla,

2012). Hexane extract of *A. graveolens* seeds contains β -selinene, 3-*n*-butyl-4,5-dihydrophthalide, 5-allyl-2-methoxyphenyl (Momin et al., 2000). The roots also contain erudilide, ligustilide, and senkyunolide. The compounds celeroin, vallein, and nodakenin have been isolated from the seeds. The other constituents present in essential oil are *n*-pentyl cyclohexadiene 0.9%, *n* pentyl benzene 1.7%, β -caryophyllene 0.5%, α -terpineol 0.7%, β -pinene 0.5% and myrcene 1.2% (Gupta et al., 2019; Kavalali and Akcasu, 1985) choline derivatives like choline ascorbate are also available from the plant (Figure 17.1).

17.3 PHARMACOLOGICAL ACTIVITIES

Pharmacological activities of *Apium graveolens* have been reviewed by Fazal and Singla (2012), Al-Snafi (2014) and Roper et al. (2017).

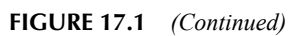
17.3.1 Anti-Diabetic Activity

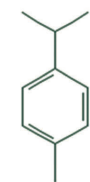
The effect of *A. graveolens* leaf alcoholic extract on blood glucose and plasma insulin levels in elderly pre-diabetics was investigated by Yusni et al. (2018). Treatment involved capsules at the dose of 250 mg, 3 times per day (morning, afternoon, and evening), 30 minutes before a meal, for 12 days. Results showed a substantial decrease in pre-prandial plasma glucose levels and post-prandial plasma glucose levels, but no significant rise in plasma insulin levels following treatment with elderly pre-diabetics.

17.3.2 Anti-Adhesive and Anti-Quorum Activity

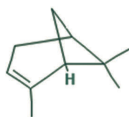
Grube et al. (2019) investigated the potential anti-adhesive activity of *A. graveolens* fruit acetone and hydroalcoholic extracts using adhesion of fluorescent-labeled uropathogenic bacteria (Uropathogenic *Escherichia coli* Strain NU 14 (UPEC NU14) to T24 bladder cells. *A. graveolens* extract showed concentration-dependent anti-adhesive activity (IC_{50} 85 μ g/mL), due to the presence of the phthalides senkyunolide sedanenolide.

Sarshar et al. (2018) investigated the anti-adhesive and anti-quorum sensing effect of hydroalcoholic extract of *A. graveolens* targeting UPEC (Strain NU14) and human T24 bladder cells and *in vivo* studies carried out on UPEC infection model using BALB/c mice. The influence of the extract

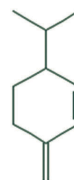




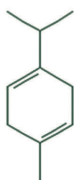
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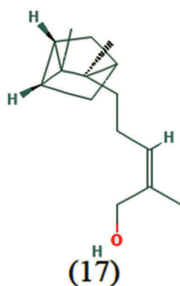
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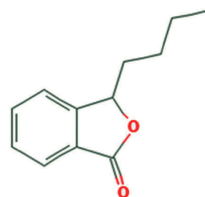
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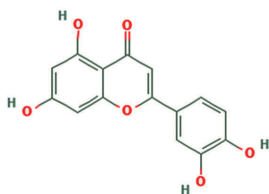
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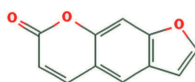
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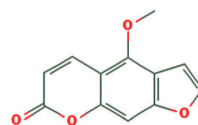
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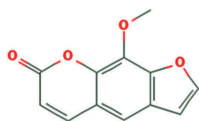
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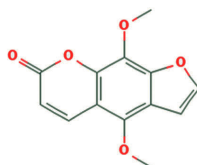
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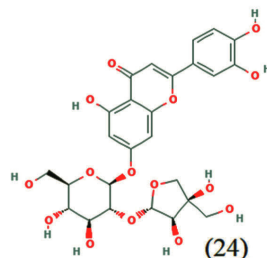
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FIGURE 17.1 Structures of: (1) Celerin; (2) bergapten; (3) apiumoside; (4) epiumetin (5); celeroside (6); apigenin (7); isoquercitrin (8); phytic acid (9); selenine (10); limonene (11); β -pinene (12); camphene (13); cymene (14); α -pinene (15); β -phellendrene (16); γ -terpinene (17); santalol (18); 3-n-butylphthalide (19); luteolin (20); psoralen (21); bergapten (22); xanthotoxin (23); isopimpinellin (24); graveobioside A.

(200, 500 mg/kg) on bladder tissue bacterial load was assessed within 4 and 7 days of pretreatment of the animals. Extract showed concentration-dependent anti-adhesive effect on UPEC strains and inhibited in a concentration-dependent manner bacterial quorum sensing. *In vivo* results reported that significantly reduced the bacterial load in bladder tissue. *A. graveolens* hydroalcoholic extract is assessed as an antiadhesive extract for which the traditional use in phytotherapy for urinary tract infection (UTI) is justified.

17.3.3 Anti-Hyperlipidemic Activity

A. graveolens seeds chloroform fractions and isolated compounds seselin, methoxsalen, and 3H-isobenzofuran-1-one at the oral dose of 50 mg/kg were tested for antihyperlipidemic activity on Triton WR 1339 induced hyperlipidemia (Iyer et al., 2019). Study results showed a reduction in total cholesterol, triglycerides, and low-density lipoprotein (LDL) level and significantly increased high density lipoprotein (HDL) level after the treatment on hyperlipidemic rats. Kamal et al. (2009) study investigated hypolipidemic effects of ethanol extract of *A. graveolens* L (213 or 425 mg/kg B.Wt.) in rats. Extract showed a significant decrease of serum total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-c), and a significant increase in high-density lipoprotein cholesterol (HDL-c) in the treated groups. *A. graveolens* (celery seeds) ethanolic extract doses (75 mg/kg, 150 mg/kg) showed significant hypolipidemic effect on ritonavir induced hyperlipidemic mice (Ahmed and Sayedda, 2012). Hydroalcoholic extract. Graveolens (100 and 200 mg/kg/BW) substantially decreased cholesterol and LDL but did not have substantial effects on high fat diets fed to rats in serum triglyceride, HDL, and VLDL (Kooti et al., 2014). Aqueous celery extract has been treated intraperitoneally to genetically hypercholesterolemic (RICO) and normocholesterolemic (RAIF) rats. Tsi et al. (1995, 1996, 2000) showed that the serum cholesterol concentration of the celery extract-treated RICO rats was found to be significantly lower through increased bile acid excretion and no such observation was seen in the RAIF rats.

17.3.4 Antitumor Activity

A. graveolens seeds chloroform fractions and isolated compounds seselin, methoxsalen, and 3H-isobenzofuran-1-one at the oral dose of 50 mg/kg were tested by Iyer et al. (2019) for antitumor activity on B16F10 melanoma.

Results showed delay in tumor growth by increasing the volume doubling time (VDT) and growth delay (GD). Sivashanmugam and Jagannath et al. (2011) study investigated the anti-proliferative effect of the *A. graveolens* methanolic extract *in vitro* on DLA, Dalton's lymphoma ascites; L929, Mouse lung fibroblast human cell lines. The extract was found to be cytotoxic towards L-929 cells in 72 hrs MTT assay and the concentration required for 50% cell death was 3.85 µg/ml. This study confirms that methanolic seed extract of *A. graveolens* possess cytotoxicity and provoke DNA fragmentation, a sign of induction of apoptosis.

Wood et al. (2001) assessed the safety mechanisms of sedanolide (100 microM for 24 h) of celery seed oil on hydrogen peroxide (H_2O_2)-and tert-butyl hydroperoxide (tBOOH)-induced toxicity in HepG2 and CaCo-2 cells. The result of this study revealed that not harm to cells in culture, but that protection was not statistically significant.

17.3.5 Effect on Polycystic Ovary Syndrome

Khodaeifar et al. (2019) investigated the effect of *A. graveolens* hydroalcoholic extract on metabolic alteration and ovarian oxidative injury in polycystic ovarian syndrome (PCOS) rats. At the dose of 200 mg/kg of *A. Graveolens* significant regulation of serum fast blood sugar (FBS), insulin, lipid profile, and oxidative stress markers in the alleviation of PCOS problems.

17.3.6 Anti-Epileptic Activity

A. graveolens seeds contain L-3-n-butylphthalide (NBP) as an active molecule which has showed epileptic activity using pilocarpine-induced chronic epileptic mouse model, NBP treatment increased the transcription of neuroprotective factors, brain-derived neurotrophic factors. These findings suggest that NBP treatment may be a potential strategy for ameliorating epileptogenesis and the comorbidities of cognitive and psychological impairments (Ye et al., 2018).

17.3.7 Hypouricemic Agent

Aim of the study is to investigate *A. graveolens* hydroalcoholic extract doses (250, 500, and 1,000 mg/kg for two weeks) effect against potassium oxonate induced hyperuricemia in mice. The data also showed that the *A. graveolens*

hydroalcoholic extract treatment inhibit the potassium oxonate increase in serum uric acid (UA) level, liver XO/XDH activities, respectively, and hepatic lipid peroxides levels (Dolati et al., 2018).

17.3.8 Anti-Hypertensive Activity

Madhavi et al. (2009) evaluated the antihypertensive effect of a celery extract (150 mg/d), supplying 85% 3-n-butylphthalide (3nB) in 30 milds to moderate hypertensive patients given the test medication following a 7-day washout period. There was a statistically significant decrease in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) at week 3 and week 6 compared to baseline. The change at week 6 for the SBP was 8.2 mmHg and for the DBP was 8.5 mmHg. The results from this pilot study suggest that celery seed extract may have clinically relevant blood pressure (BP)-lowering effects.

A. graveolens leaf extract and captopril combination will be helpful for the treatment of hypertension, as it shows an increase in plasma level of captopril leads to improvement in its efficacy (Siska et al., 2018).

17.3.9 Anti-Arthritic Activity

Choosri et al. (2017) investigated the effects of an *A. graveolens* extract on the arthritis in rats induced using complete Freund's adjuvant (CFA) and results was significantly attenuated the severity of CFA-induced arthritis by decreased the arthritis score, paw, and ankle thickness and antioxidant status was significantly increased.

A. graveolens seed extract (30 g/BID) treated chronic osteoarthritis diseases horse improved amplitude, sensitivity to passive flexion and flexion correlated with a lower perception of the pain and the effects were compared with a standard NSAID drug (Battaglia et al., 2019).

17.3.10 Improvement in Cognitive Function and Antidepressant

Boonruamkaew et al. (2017) study results execute that the *A. graveolens* enhancing cognitive function and antidepressant by reducing the MAO-A neurotransmitter system, cognitive-enhancing effects associated with decreased

AChE activity, antioxidant pathway related to a decrease of the MDA level, and inhibition percentage of the O_2 -while increasing GPx activity.

Srinivasa et al. (2012) tested the antidepressant effect of *A. graveolens* seeds (AGM) methanolic extract using the forced swim test (FST) and tail suspension test (TST) in mice. Results showed that the *A. graveolens* seeds (200 mg/kg B.Wt.) possessed significant antidepressant activity in animal models.

17.3.11 Spasmolytic Activity

A. graveolens leaves aqueous and ethanol extracts showed spasmolytic activity on rat ileum contractions (Brankovic et al., 2015). The results obtained in this work showed that the ethanol extracts of *A. graveolens* (1–3 mg/ml) leaves can inhibit spontaneous ileum contractions and contractions induced by acetylcholine, significant higher compare to aqueous extract. Spasmolytic effect may be due to blockade of muscarinic receptors on ileum.

17.3.12 Larvicidal Activity

Kumar et al. (2014) investigated larvicidal efficacy of *A. graveolens* seed oil (99%, 1 ml) against dengue fever mosquito *Ae. aegypti*. The larval mortality was monitored by determining the movements of the larvae after 24 h of intervention by gently touching the larvae with the aid of a glass rod and results were showed that low LC_{50} and LC_{90} values of 16.10 and 29.08 ppm, respectively. The toxicity ability of the oil increased by 1.2-fold ($LC_{50} = 13.22$ ppm) after exposure of the larvae to the oil for another 24 hours (Kumar et al., 2014). Ethanolic extract of *A. graveolens* reported larvicidal effect on *Ae. aegypti* larvae with LD_{50} and LD_{95} values of 81.0 and 176.8 mg/L, respectively (Choochote et al., 2004).

17.3.13 Anti-Fertility Activity

Al-Sanabra et al. (2013) evaluated the effect of *A. graveolens* seed ethanolic extract (two doses 425 and 213 mg/kg bodyweight for 60 consecutive days) on male rat fertility. Study results showed arrested spermatogenesis and caused a marked, dose-dependent decrease in sperm count, cauda epididymal sperm motility, blood testosterone concentration, weight of testes and seminal vesicles, testicular protein content as well as diameter and

viability of seminiferous tubules. In addition, a lower number and weight of viable fetuses was obtained for female rats which were impregnated by extract-treated male rats (Al-Sanabra et al., 2013).

17.3.14 Cardiac Protective Activity

Kolarovic et al. (2009) investigated the protective effect of *A. graveolens* leaves and roots juices (5% solution (v/v), 4 times in a day, 14 days treatment) in doxorubicin-induced cardiac toxicity on rats. *A. graveolens* and leaves juices treatment results showed protective effects against doxorubicine by improving liver and blood antioxidant parameters.

17.3.15 Anti-Inflammatory Activity

Aqueous extracts of celery stem have been investigated by Lewis et al. (2008) and found to have significant anti-inflammatory activity against two animal models. Apiuman is a pectic polysaccharide from *A. graveolens* stalks was investigated for anti-inflammatory activity against lipopolysaccharide induced inflammation on Male A/HeJ mice. Apiuman (200 μ L) prevents of lipopolysaccharide induced inflammation by decrease the interleukin-1 β and increased interleukin-10 production and diminish the neutrophils migra due to potential Apiuman (Ovodova et al., 2009).

17.3.16 Analgesic Activity

Ramezani et al. (2009) investigated the antinociceptive and anti-inflammatory effects of the aqueous and hexane extracts obtained from *A. graveolens* seeds were evaluated against formalin and xylene-induced ear edema. Hexane fraction reduced the nociception produced by formalin solution in the first phase (0–5 min) at 300, 400, and 500 mg/kg BW, and in the second phase (20–30 min) at 500 mg/kg BW. Results concluded that the hexane fraction has a major contribution to the overall antinociceptive activity.

17.3.17 Hepatoprotective Activity

A. graveolens seed methanolic extract was found to have shown acceptable protective activity against paracetamol (PCM)-induced (Singh and Handa,

1995) and carbon tetrachloride-induced (Ahmed et al., 2002) liver damage, also it is reported that the combination of *A. graveolens* and chicory and barley attenuates the elevated serum liver enzymes, total cholesterol, triglycerides, and improves lipid profile in cholesterol-fed diets (Abd El-Mageed et al., 2011).

17.3.18 Anti-Ulcer Activity

Methanolic and aqueous extracts of *A. graveolens* aerial part and seed 300 mg/kg dose exhibited a highly significant inhibition of gastric lesions (91% and 95%, respectively) on HCl/EtOH solution induced ulcers (Baananou et al., 2013).

17.3.19 Antibacterial Activity

Baananou et al. (2013) evaluated the antibacterial activity of *A. graveolens* essential oil (concentration 100, 50, 25, 12.5, 6.3, 3.3, 1.6, 0.8, 0.4, and 0.2%) against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The essential oil showed zone of inhibition (ZI) 30 mm, 17 mm and 25 mm, respectively. *A. graveolens* extract exhibited antibacterial activity against strains such as *E. coli* (5.6 mg/ ml) and *S. aureus* (4 mg/ mL) in comparison with *P. aeruginosa* (16.5 mg/ mL).

17.3.20 Effect on Male Hormones

Kooti et al. (2015) investigated the effect of hydro-alcoholic extract of celery leaf (200 and 300 mg/kg/B.W) on serum levels of FSH and testosterone. Results did not show any significant difference with the control and placebo groups. It seems that consumption of this plant does not cause any hormonal impairment in males; and probably does not have any side effect on the fertility.

17.3.21 Mosquitocidal, Nematicidal, and Antifungal

Momin and Nair (2001) investigated the effect of *A. graveolens* seeds bioactive methanolic extract and bioactive compounds mosquitocidal,

nematicidal, and antifungal activity. Bioactive compounds were confirmed as sedanolide, senkyunolide-N, and senkyunolide. They performed mosquito-cidal assay on mosquito larvae, *Aedes aegyptii*, Nematicidal Assay on *Panagrellus redivivus* and *Caenorhabditis elegans*, and antifungal assay on *Candida albicans* and *Candida parapsilasis*. At 100 $\mu\text{g mL}^{-1}$, senkyunolide-N, and senkyunolide-J showed 100% mortality when tested against *P. redivivus*. Sedanolide gave 100% mortality at 50 $\mu\text{g/ml}$ when tested on fourth-instar *A. aegyptii* larvae. Only sedanolide gave zones of inhibition of 11 mm each for *C. albicans* and *C. parapsilasis* at 100 $\mu\text{g/ml}$ on culture plates.

17.3.22 Phytophotodermatitis

Preliminary experiments celery marketed formulations have estimated psoralen levels as high as 25 $\mu\text{g/cm}^2$ of trimmed surface. Results concluded that phytophotodermatitis among food processors can be caused by healthy celery and outcome from a complex interaction of exposure variables such as ultraviolet radiation (Seligman et al., 1987).

17.3.23 Anti-Platelet Aggregation

Teng et al. (1988) evaluate anti-platelet aggregation activity of Apigenin, a constituent of *A. graveolens*. Results exhibited that Apigenin (IC_{50} -50 $\mu\text{g/ml}$) inhibits collagen-induced platelet aggregation, and also inhibited the release of ATP from platelets induced by all aggregates used.

17.3.24 Antibacterial and Spasmolytic Activity

The study tested *Apium graveolens* antibacterial sensitivity on *E. coli* and spasmolytic effect on contraction of isolated rabbit jejunum. Results revealed that *Apium graveolens* showed a wide ZI of *E. coli* growth in concentration of 5% and caused relaxation of spontaneous contractions of isolated rabbit jejunum (Naema et al., 2010). Hassanen et al. (2015) study results concluded that celery herb and seed essential oils exhibited significant antimicrobial activity of different concentrations (0.3, 0.6, 0.9, 10, 50 and 100%) by using the disc diffusion method.

KEYWORDS

- fast blood sugar
- growth delay
- high density lipoprotein
- low-density lipoprotein
- polycystic ovarian syndrome
- urinary tract infection
- *Apium graveolens*

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CHAPTER 18

A Review on Phytochemistry and Pharmacology of *Rivea hypocrateriformis* (Desr.) Choisy

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18.1 INTRODUCTION

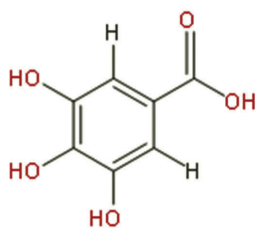
Rivea hypocrateriformis (Desr.) Choisy is an important member of family Convolvulaceae, reported from subtropical forests of India, Pakistan, and Afghanistan in the rainy season. It is a perennial twinning climber; the vine is strong, woody, and rises up to 4 meters and is locally known as Phang, Midnapore Creeper, Night glory, Vaividang (Brahmbhatt et al., 2010; Al-Baadani and Satyanarayan, 2018; Dhore, 1986). In many parts of India, leaf, and young shoots are consumed as raw vegetables. Leaf juice is applied to treat hair and scalp-related disorders. Oral dose of leaves juice in cow milk is consumed to overcome rheumatic pain (Anonymus, 2001; Kirtikar and Basu, 1968). Its root is used against snakebites (Suthari et al., 2014).

18.2 BIOACTIVES

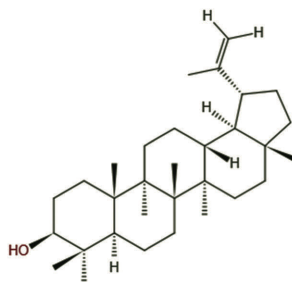
Phytochemical screening revealed the presence of steroid, tannins, terpenoids, alkaloids, coumarin, phytosterols, and phenolic compounds from *R. hypocrateriformis* (Khandekar et al., 2015; Kukkar et al., 2018; Smitha et al., 2012). Additionally, methanolic leaves extract of *R. hypocrateriformis* documented flavonoids, glycosides, and saponins (Al-Baadani and Satyanarayan, 2018). 95% ethanol extract of *R. hypocrateriformis* aerial parts tested positive for alkaloids, glycosides, saponins, tannins, and phenolic compounds

(Shivalingappa et al., 2001). Phytochemical examination revealed the presence of alkaloids, proteins, glycosides, tannins, anthocyanins, quinones, and flavonoids from roots (Jyothirmai et al., 2014). Phytochemical evaluation of aerial parts using petroleum ether, chloroform, ethanol, and aqueous extract reported a significant amount of flavonoids, alkaloids, steroids, and phenolic compounds (Saboo et al., 2014). Gallic acid, lupeol, and other polyphenolic compounds were identified by HPLC analysis from successive ethanol extracts of *R. hypocrateriformis* aerial parts (Saboo et al., 2011). Quercetin was isolated from aerial parts of *R. hypocrateriformis* (Godipurge et al., 2016). Rivebergenin A, Rivebergenin B, Bergenin, and Norbergenin compounds were isolated from *R. hypocrateriformis* stem, notably first two compounds were derivatives of Bergenin (Zamarrud et al., 2011). FTIR analysis of *R. hypocrateriformis* whole plant documented various functional groups viz. phenols, alkanes, nitro compounds (oxime and lactams), ethers, aromatic compounds and halogen derivatives (chloro-compounds and bromo-compounds) (Shalini, 2018). GCMS analysis of *R. hypocrateriformis* leaves extract reported compounds like, 4,25-Secobscurinervan,21-deoxy-16-methoxy-22-methyl; [-(+)-Ascorbic acid 2,6-dihexadecanoate; Cis,trans-5,{9-Cyclododecadienecis-1,2-diol; oleic acid; rescinamine; estra-1,3,5(10)-trien-17a-ol; pregn-5-ene-3,11-dione,17,20;20,21-bis[methylenenbis(oxy)]-cyclic3-9(1,2-ehanediyol acetol); 3,8,8-Trimethoxy-3-piperidyl-2,2'-binaphthalene-1,1',4,4'-tetrone (Khandekar et al., 2015). LCMS analysis of *R. hypocrateriformis* aerial parts reported 34 compounds viz, proansamitocin, symlandine, (4E,6E,d14:2) sphingosine, 2-hexyl-decanoic acid, cochlearine, 2,2,4,4-tetramethyl-6-(1-oxopropyl)-1,3,5-cyclohexanetrione,6-C-glucopyranosylpilloin,3-hexanoyl-NBD cholesterol, artelastochromene, 8-trans-[2-(6-Benzoyloxy-4-hydroxy-2-methoxy-3-methylphenyl)ethenyl]-5-methoxyflavan-7-ol, Arg Arg Gln, 8-hydroxyluteolin 8-glucoside, GlcAbeta-Cer(d18:1/18:0), 4-methyl-aminobutyrate, 6-C-glucopyranosylpilloin, N-cyclohexylformamide, 8E-tetradecenyl acetate, Ala His Asn, Trp Arg Asp, 3'-deoxymaysin, 3-hydroxycoumarin, 14,14,14-trifluoro-11E-tetradecenyl acetate, spectinomycin, 14,14,14-trifluoro-11E-tetradecenyl acetate, lymecycline, 5Z-tridecene, lauroyl-EA, 16-hydroxy hexadecanoic acid, decenedioic acid, dicyclohexylamine, 3,4-dihydroxyphenyl ethanol, crotamiton, 10E,12Z-tetradecadienyl acetate and labienoxime (Patel et al., 2019a). Total 46 compounds were extracted from *R. hypocrateriformis* leaves using Liquid Chromatogram-Mass Spectrometry (Patel et al., 2019b). LCMS analysis of *R. hypocrateriformis* root reported 54 compounds (Patel et al., 2018a). Two

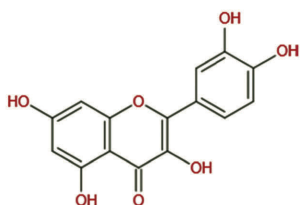
novel alkaloids extracted from aerial parts of *R. hypocrateriformis* and are defined as hypocretine 1 and 2 (Godipurge et al., 2018). From methanol extract of *R. hypocrateriformis* aerial parts desmethylbergenin hemihydrate (3,4,8,9,10-pentahydroxy-2-hydroxymethyl-2,3,4,4a,6,10b-hexahydropyrano[3,2-c]isochromen-6-one hemihydrate) a derivative of bergenin was isolated (Figure 18.1) (Zamarrud et al., 2006).



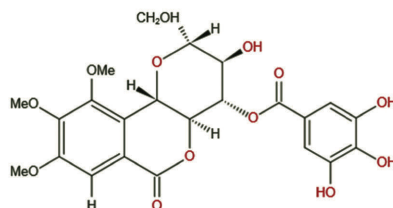
Gallic acid



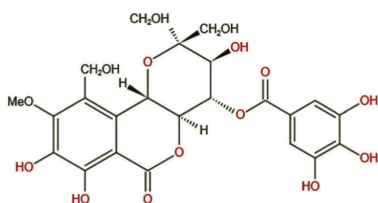
Lupeol



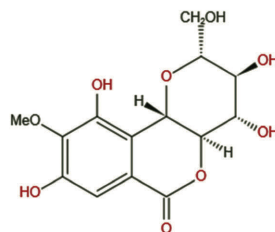
Quercetin



Rivebergenin A

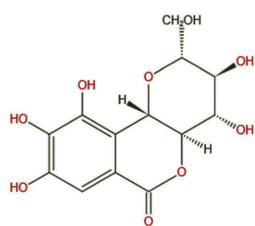


Rivebergenin B

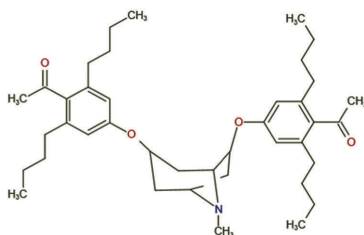


Bergenin

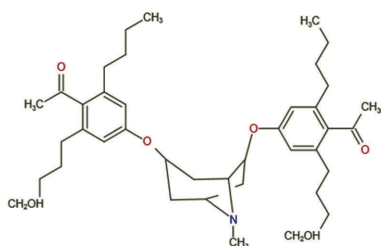
FIGURE 18.1 (Continued)



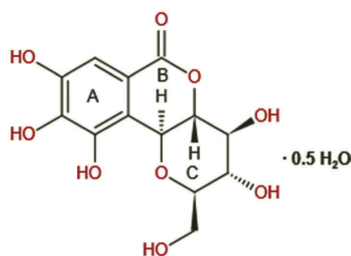
Norbergenin



Hypocretine compound 1



Hypocretine compound 2



Desmethyllbergenin hemihydrate

FIGURE 18.1 Phenolic acid, triterpenoid, flavonoid, glycoside, alkaloid, and isocoumarin compounds from aerial parts and stem of *Rivea hypocrateriformis* (Saboo et al., 2011; Fahmy et al., 2015; Amoussa et al., 2016; Zamarrud et al., 2006, 2011; Godipurge et al., 2016, 2018).

18.3 PHARMACOLOGY

18.3.1 Antibacterial Activity

Aqueous extract of *R. hypocrateriformis* leaves showed the highest zone of inhibition (ZI) of 18 ± 0.3 mm against *E. coli* while least ZI of 08 ± 0.5 mm reported by chloroform extract against *S. aureus*. Notably DMSO extract showed consistent ZI against all 5 microbial species (Khandekar et al., 2015). Disc diffusion method revealed chloroform extract of aerial parts significantly inhibited the growth of *S. aureus* and *B. subtilis*, whereas aqueous extract strongly retards the growth of *E. coli*, *P. aeruginosa*, *P. vulgaris* (Saboo et al., 2014). Crude methanolic root extract significantly inhibited the growth of *E. coli*, *B. subtilis*, *B. cereus*, *S. aureus*, *P. aeruginosa*, *P. vulgaris* and *Salmonella* spp. (Smitha et al., 2012). The growth of *S. aureus* and *E. coli* were inhibited by methanolic extract of aerial parts, leaves, and roots; among them leaves reported the highest antibacterial potential (Patel et al., 2018b).

18.3.2 Antifungal Activity

Aqueous as well as methanol extracts of *R. hypocrateriformis* aerial parts significantly inhibited growth of *Aspergillus niger*, *Candida albicans* and *Aspergillus flavus* (Saboo et al., 2014). Crude methanolic root extract inhibited growth of *Trichoderma viride* and *Penicillium* species, whereas it failed to do so with *A. niger* (Smitha et al., 2012). *A. niger* growth was inhibited by methanolic extract of *R. hypocrateriformis* leaves, roots, and aerial parts at all concentrations (Patel et al., 2018).

18.3.3 Antioxidant Efficacy

DPPH free radical scavenging activity of *R. hypocrateriformis* methanolic leaves extract reported with IC_{50} value of 4147 $\mu\text{g/ml}$ (Khandekar et al., 2015). Crude methanolic root extract exhibited excellent antioxidant potential in FRAP assay with 47.6 mg GAE/g of sample (Smitha et al., 2012). Acetone extract of *R. hypocrateriformis* leaf, stem, and flower showed potent antioxidant activity with IC_{50} of 0.1 mg/ml using DPPH assay; also, significant metal chelating activity revealed by methanol extracts of leaves and stem with 162.0 and 169.8 mg EDTA/g extract, respectively, and in FRAP assay, methanol extract of flower showed highest antioxidant activity as 1,127.1 $\mu\text{mol Fe(II)/g}$ extract (Loganayaki et al., 2010). Ethanolic extracts of *R. hypocrateriformis* showed good antioxidant activity in DPPH assay ($R^2 = 0.403$) (Sudhanshu et al., 2012). Successive ethanol extracts number 2 of *R. hypocrateriformis* aerial parts revealed best substantial free radical scavenging activity in ABTS, DPPH, Lipid peroxide and superoxide assays with IC_{50} values of 30.49 ± 1.09 , 22.06 ± 0.27 , 25.54 ± 0.11 and 28.08 ± 0.05 $\mu\text{g/mL}$, respectively (Saboo et al., 2011). Etanolic extract of *R. hypocrateriformis* aerial parts recorded potent antioxidant activity than standard ascorbic acid in the DPPH assay ($IC_{50} = 43.23$ and 46.70 $\mu\text{g/mL}$, respectively) (Godipurge et al., 2015). Polyphenolic fraction of aerial parts exhibited potent antioxidant activity in the lipid peroxidation and hydroxyl radical scavenging activity assay (76 and 76.5% scavenging activity) (Godipurge et al., 2016). Rivebergenin A, rivebergenin B, bergenin, and norbergenin compounds extracted from *R. hypocrateriformis* stem exhibited strong antioxidant activity in the DPPH assay with high percentages of inhibition (84.1, 83.3, 81.8 and 85% respectively) (Zamarrud et al., 2011). In DPPH radical scavenging assay, aqueous leaves extract reported effective scavenging activity with IC_{50} of

254 \pm 5.29 μ g/mL and total antioxidant activity measures 111.30 \pm 0.003 mcg (Borkar et al., 2015). Methanol extracts of root revealed moderate antioxidant potential (IC₅₀ = 523.64 μ g/mL) when subjected for DPPH assay (Smitha et al., 2013).

18.3.4 Hepatoprotective Activity

About 100 mg/kg body weight of successive ethanolic extract of *R. hypocrateriformis* revealed highest hepatoprotective activity which was found parallel to that of standard silymarin; also, liver samples treated with this extract were found to protect from CCl₄ induced hepatotoxicity, with no sample with necrosis features. Hindrance of lipid peroxidation was evident by declined MDA and elevated SOD, CAT, and GSH levels after treatment with ethanolic extract (Saboo et al., 2011). Paracetamol (PCM) induced serum ascend of ALT, AST, ALP, and TB were significantly reduced at 300 and 600 mg/kg doses of polyphenolic fraction of aerial parts of *R. hypocrateriformis* (Godipurge et al., 2016).

18.3.5 Analgesic Activity

R. hypocrateriformis ethanolic leaves extract at 200 and 400 mg/kg doses extensively found to suppress carrageenan-induced paw edema in albino rats (Brahmbhatt et al., 2010). Ethanolic extract of *R. hypocrateriformis* aerial parts at 200 and 400 mg/kg of body weight inhibited paw edema by 28.57 and 71.42% respectively after 4 hours and in hot plate and tail-flick tests showed lengthened potential increased pain threshold period of both mice and rats (Godipurge et al., 2015). On testing of analgesic action by acetic acid-induced method, ethanolic extract of *R. hypocrateriformis* roots revealed 35.76 and 80.47% inhibition of writhing movements at doses of 200 and 400 mg/kg of body weight (Jyothirmai et al., 2014).

18.3.6 Anti-Inflammatory Activity

At the end of 3 hours, *R. hypocrateriformis* ethanolic leaves extract at 200 and 400 mg/kg of body weight exhibited 64.83 and 100% inhibition of paw edema, respectively (Brahmbhatt et al., 2010).

18.3.7 Anti-Tubercular Activity

Anti-tubercular activity of n-hexane, DCM, and methanol extracts of *R. hypocrateriformis* on *Mycobacterium tuberculosis* using micro-plate Alamar blue assay (MABA) method depicted activity at 12.5 µg/ml concentration (Al-Baadani and Satyanarayan, 2018).

18.3.8 Anti-Arthritic Activity

R. hypocrateriformis leaves methanolic extract at 250 and 500 mg/kg, p.o revealed significantly reduction in the arthritic index as compared to control group; also, at same dose reduction in the level of SGOT, SGPT, and ALP enzymes level was recorded (Kukkar et al., 2018).

18.3.9 Anti-Fertility Activity

In albino rats, ethanolic extract of *R. hypocrateriformis* aerial parts at a dose of 200–400 mg/kg/body weight was found to exhibit disruption of the estrous cycle and decrease in graffian follicles as well corpora lutea (Shivalingappa et al., 2002). Ethanolic extract of *R. hypocrateriformis* aerial parts at 400 mg/kg body weight in female albino rats exclusively inhibited pregnancy in all 5 rats with a mean number of implants 5.4 and interrupted the pregnancy in all 5 rats of a group (Shivalingappa et al., 2001). 95% alcoholic extract of *R. hypocrateriformis* whole plant at 200 and 400 mg/kg body weight in female albino rats revealed 66 and 100% antiimplantation activity, respectively, and reversed activity was notices on taking out extract treatment (Shivalingappa et al., 1999).

18.3.10 Antihemolytic Activity

Crude extract and hypocretine 1 and 2 extracted from aerial parts of *R. hypocrateriformis* tested against cow erythrocytes. Crude extract depicted the lowest antihemolytic activity, whereas at a higher dose of 250 g/mL, hypocretine 1 and 2 revealed 74 and 79% antihemolytic activity, respectively, and both showing IC₅₀ values of 50 g/mL (Godipurge et al., 2018). The highest 33% of antihemolytic activity was recorded in acetone extract of *R. hypocrateriformis* leaves (Loganayaki et al., 2010).

18.3.11 Cytotoxic Activity

Crude extract and hypocretine 1 and 2 extracted from aerial parts of *R. hypocrateriformis* were evaluated to determine cytotoxicity against MCF-7 breast cancer cell line using MTT assay. Cell viability at 50 g/mL for crude extract, hypocretine 1 and 2 was found to be 69, 52, and 50%, respectively, which drops further to 38, 30, and 34% respectively after 24 h exposure at 250 g/mL. Also, for crude extract and hypocretine 1 and 2, after 24 h exposure the recorded IC₅₀ values are 150 and 50 g/mL, respectively (Godipurge et al., 2018).

18.3.12 Antimitotic Activity

Successive chloroform and ethanol extract of *R. hypocrateriformis* aerial parts significantly inhibit meristematic cells of *Allium cepa* roots with mitotic index of 14.24 and 12.14, respectively (Saboo et al., 2012).

18.3.13 Antiproliferative Activity

The viable cell count for successive chloroform and ethanol extract of *R. hypocrateriformis* was measured to be 282×10^3 and 283×10^3 cells/mL, respectively, and IC₅₀ values were found to be 47.88 and 27.12 mg/mL, respectively (Saboo et al., 2012).

18.3.14 Anticancer Activity

Successive chloroform and ethanol extract of *R. hypocrateriformis* whole plant exhibited potent anticancer activity against leukemia, MOLT-4 and breast cancer cell line, MCF-7. Both extracts depict moderate activity against lungs cancer cell line, HOP-62 but found ineffective against Prostate, PRO, and Colon, HCT-15 cancer cell lines (Saboo et al., 2012).

18.3.15 Anticonvulsant Effect

Ethanol extract of *R. hypocrateriformis* fruits given as oral dose of 62.5–125 mg/kg revealed anticonvulsant effect (Dhawan et al., 1980).

18.3.16 Sedative Effect

Ethanol extract of *R. hypocrateriformis* fruits at oral dose of 62.5–125 mg/kg in mice reported sedative effect in pentobarbitone induced hypnosis models, by reducing sleep induction time and lengthening the sleep duration time (Dhawan et al., 1980).

KEYWORDS

- *Aspergillus flavus*
- Convolvulaceae
- micro-plate Alamar blue assay
- phytochemical
- *Rivea hypocrateriformis*
- zone of inhibition

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CHAPTER 19

Bioactives and Pharmacology of *Blumea lacera* (Burm.f.) DC. and *Blumea eriantha* DC.

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19.1 INTRODUCTION

Genus *Blumea* belonging to the family Asteraceae has several species with medicinal properties, and traditionally, many of the species have been used to treat different disorders ranging from expectorants to anti-cancer agents. *Blumea lacera* has been used conventionally as anti-helminthic, anti-pyretic, and diuretic (Dixit and Varma, 1976). It is also known to relieve bronchitis, burning sensation and fever (Agarwal et al., 1995). The leaves of *B. lacera* are used as anthelmintic, febrifuge, and astringent. The plant is a diuretic, antiscorbutic, and useful in catarrhal affections (Ragasa et al., 2007). *Blumea eriantha* has been used as a diuretic and for the treatment of cholera and diarrhea in traditional medicines (Khare, 2007; Singh et al., 2012). The leaves and stem were used to extract essential oils, which have demonstrated potent antibacterial, antifungal, and insecticidal properties (Khare, 2007; Singh et al., 2011).

19.2 BLUMEA LACERA

19.2.1 Bioactives

Agarwal et al. (1995) reported isolation of glycosides, namely, the triterpenoid glycoside 19 α -hydroxyurs-12-ene-24,28-dioate 3-O- β -d-xylopyranoside and the phenol glycoside 2-isoprenyl-5-isopropylphenol 4-O- β -d-xylopyranoside from the whole plant of *B. lacera*. 5-Hydroxy-3,6,7,3',4'-pentamethoxyflavone

and 5,3,4'-trihydroxy-3,6,7-trimethoxyflavone have been isolated from the leaves of *B. lacera* (Rao et al., 1977). In yet another study, using the leaves of *B. lacera*, α -pinene-7 β -O- β -D-2,6'-diacetylglucopyranoside, 5'4'-dihydroxy-6,7,3'-trimethoxy flavone, and 3,5,4'-trihydroxy-6,7,3'-trimethoxyflavone were isolated (Ragasa et al., 2007). The structures are depicted in Table 19.1.

Methanol extract of *B. lacera* showed the presence of carbohydrate, reducing sugar, phytosterols, coumarin, tannins, phenolic compounds, saponins, amino acids, steroids, and flavonoids. Other compounds such as β -caryophyllene, thymol hydroquinone, dimethylether, caryophyllene oxide, α -humulene, E- β -farnesene, 19- α -hydroxy-12-ene-24, 28-dioate-3-O- β -D-xylopyranoside, 2-isoprenyl-5-isopropylphenol-4-O- β -D-xylopyranoside, 5-hydroxyl-3,6,7,3,4'-pentamethoxy flavone, 5,3,4'-trihydroxy-3,6,7-trimethoxyflavone, campesterol, and a coniferyl alcohol derivative were isolated from the methanolic leaf extract (Hasan et al., 2015). 21 compounds have been isolated from different parts of *B. lacera*, such as flavonoids, terpene glycosides, phenol glycosides, sterols, essential oils, coniferyl alcohol derivatives, terpenoid ketones and steroidal glycoalkaloids. Two diterpenoid glycosides and two flavonoid glycosides, including the new diterpenoid glycoside 6E,10E,14Z-(3S)-17-hydroxygeranyllinalool-17-O- β -D-glucopyranosyl-(1 \rightarrow 2)-[α -l-rhamnopyranosyl-(1 \rightarrow 6)]- β -D-glucopyranoside, 3-O- β -D-glucopyranosyl-6E,10E,14Z-(3S)-17-hydroxygeranyllinalool-17-O- β -D-glucopyranosyl-(1 \rightarrow 2)-[α -l-rhamnopyranosyl-(1 \rightarrow 6)]- β -D-glucopyranoside, kaempferol 3-O-(2,6"-di-O- α -rhamnopyranosyl)- β -galactopyranoside and kaempferol-3-O- α -L-rhamnopyranosyl-(1 \rightarrow 6)- β -D-glucopyranoside were obtained from the methanolic extract of leaves of *B. lacera* (Akter et al., 2016). The structures are shown in Table 19.1.

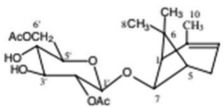
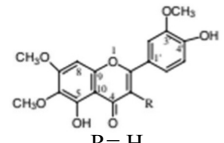
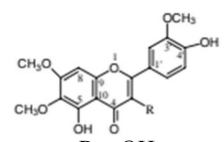
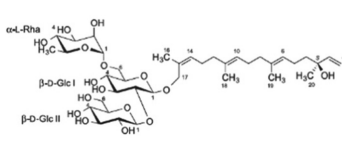
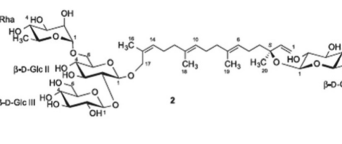
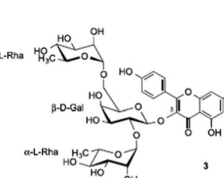
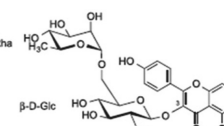
19.2.2 Pharmacology

19.2.2.1 Anti-Diabetic Effect

Methanol leaf extract of *B. lacera* exhibited glucose lowering in a dose-dependent manner, and 46.85% hypoglycemic activity was detected with the extract at a dose of 400 mg/Kg compared to the standard drug glibenclamide which showed 47.53% at dose of 10 mg/kg in Swiss albino mice. It was postulated that this glucose-lowering effect could be due to the presence of tannins and flavonoids in *B. lacera* (Hasan et al., 2015). In yet another study, antidiabetic effects of methanol extract of *B. lacera* have been documented

by Rath et al. (2017). In this study, at a dose of 400 mg/kg, a fall of blood glucose of 34.68 ± 1.58 mg/dL at 3 h in normal rats and 51.88 ± 1.66 at 3 h in diabetic rats compared to the standard drug metformin (55.67 ± 1.56 mg/dL) was recorded.

TABLE 19.1 Phytochemicals in *B. lacera*

SL. No.	Chemical Compound	Chemical Structure	References
1.	α -pinene-7 β -O- β -D-2,6'-diacetylglucopyranoside		Ragasa et al. (2007)
2.	5'4'-dihydroxy-6,7,3'-trimethoxy flavone	 R = H	Ragasa et al. (2007)
3.	3,5,4'-trihydroxy-6,7,3'-trimethoxyflavone	 R = OH	Ragasa et al. (2007)
4.	6E,10E,14Z-(3S)-17-hydroxygeranyllinalool-17-O-beta-D-glucopyranosyl-(1-2)-[alpha-L-rhamnopyranosyl-(1-6)]-beta-D-glucopyranoside		Akter et al. (2016)
5.	3-O-beta-D-glucopyranosyl-6E,10E,14Z-(3S)-17-hydroxygeranyllinalool-17-O-beta-D-glucopyranosyl-(1-2)-[alpha-L-rhamnopyranosyl-(1-6)]-beta-D-glucopyranoside		Akter et al. (2016)
6.	Kaempferol-3-O-(2,6''-di-O-alpha-rhamnopyranosyl)-beta-galactopyranoside		Akter et al. (2016)
7.	Kaempferol-3-O-alpha-L-rhamnopyranosyl-(1-6)-beta-D-glucopyranoside		Akter et al. (2016)

19.2.2.2 Cytotoxicity

Extract from *B. lacera* has shown a strong cytotoxicity against the cancer cell lines with IC₅₀ values of 8.3, 17.4 and 24.9 μ M against MCF-7, MDA-MB-231 and AGS cells, respectively. Marginal cytotoxicity was reported against colon cancer cells (HT-29) with IC₅₀ value of 102.0 μ M (Akter et al., 2016). An additional study reported cytotoxicity by methanol extract from *B lacera* leaves with IC₅₀ values of 0.01–0.08 mg/mL against gastric cell lines (AGS); colon cell lines (HT-29); and breast cell lines (MDA-MB-435S) using the MTT assay (Uddin et al., 2011).

19.2.2.3 Antibacterial Activity

Antibacterial activity of methanol extract of *B. lacera* was measured by disc diffusion method and it showed the highest zone of inhibition (ZI) (14.0 mm) against *Shigella dysenteriae*, and mild activity against *Salmonella typhi*, *Bacillus cereus* and *Staphylococcus aureus* (Khair et al., 2014). Ethyl acetate (EtOAc) leaf extract of *B. lacera* showed inhibitory action against *Pseudomonas aeruginosa* (12 mm), *Staphylococcus aureus* (12 mm), *Salmonella typhi* (11 mm) and *Escherichia coli* (10 mm) (Khandekar et al., 2013).

19.2.2.4 Anti-Fungal Activity

Flavonoids from *B. lacera* demonstrated moderate anti-fungal activity against *Candida albicans* and *Trichophyton mentagrophytes* (Ragasa et al., 2007). Methanol extract of *B. lacera* leaves confirmed considerable anti-fungal activity in a dose dependent manner with percentage of inhibition against *Aspergillus flavus* of 67%, *Aspergillus niger* 42%, *Aspergillus oryzae* 43% and *Aspergillus parasiticus* 50%. Ethanolic extract of *B. lacera* showed antifungal activity with percentage of inhibition as follows: *Aspergillus flavus* 90%, *Aspergillus niger* 63%, *Aspergillus parasiticus* 45% and *Aspergillus parasiticus* 45% (Kagne et al., 2012).

19.2.2.5 Anti-Diarrheal Activity

Methanol extract of *B. lacera* at 100 and 200 mg/kg on experimental diarrheal mice significantly reduced the total number of episodes of

defecation and demonstrated a delayed onset of diarrhea in a dose dependent manner. These results were shown to be statistically significant (Khair et al., 2014).

19.2.2.6 Anti-Pyretic Activity

Methanol extract of *B. lacera* exhibited a significant lowering of experimental mice's body temperature comparable to that of the standard paracetamol (PCM) (Khair et al., 2014).

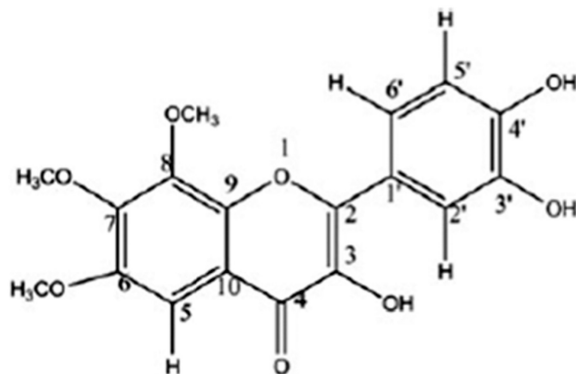
19.2.2.7 Analgesic Effect

At doses of 200 and 400 mg/kg, crude extract of *B. lacera* exhibited 39.13% and 56.52% protection, respectively, compared to 76.09% exhibited by standard diclofenac sodium. Thus, the analgesic effect was found to be significant in comparison with the standard, diclofenac sodium (Khair et al., 2014).

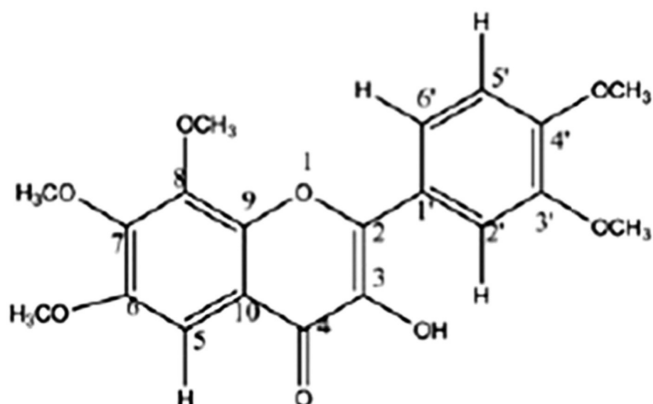
19.3 BLUMEA ERIANTHA

19.3.1 Bioactives

Two flavonoids 3,3',4'-Trihydroxy-6,7,8-trimethoxy flavone and 3-Hydroxy-6,7,8,3',4'-pentamethoxy flavones were isolated from the methanol extract of the aerial parts of *B. eriantha* (Tambewagh et al., 2019).



3,3',4'-Trihydroxy-6,7,8-trimethoxy flavone.



3-Hydroxy-6,7,8,3',4'-pentamethoxy flavones.

The compounds Ocim-(4E,6Z)-ene (13.72%), Caryophyllene (9.71%), Caryophyllene oxide (5.76%), Carvotanacetone (5.36%), Pinene (3.90%), Eudesmol (3.74%) have been isolated from the essential oils extracted from *B. eriantha* (Pednekar et al., 2013). Compounds present in the methanol leaf extract of *B. eriantha* identified on liquid chromatography coupled with mass spectrometry (LC-MS) were Liatrin, Cis-Zeatin, Buthionine sulfoximine, 12-hydroxy-jasmonic acid, Chrysosplenol C-(3,7,3'-trimethoxy-5,6,4'-trihydroxyflavone), CAY10621-[2,2-dimethyl-4S-(1-oxo-2-hexadecyn-1-yl)-1, 1-dimethylethyl ester-3-oxazolidinecarboxylic acid], 7-Methylxanthine, 5-Methoxytryptophan, CAY10603-(N-[4-[3-[[[7-(hydroxyamino)-7-oxoheptyl]amino]carbonyl]-5-isoxazolyl]phenyl]-1,1-dimethylethyl ester), Quassimarin, AG-494-(E)-2-Cyano-3-(3,4-dihydroxyphenyl)-N-phenyl-2-propenamide, 2-Naphthylalanine, Graphinone, Etanidazole (Gore et al., 2014).

19.3.2 Pharmacology

19.3.2.1 Cytotoxicity

Methanolic extracts of the leaves of *B. eriantha* demonstrated cytotoxicity against HeLa cells and B16F10 cancer cell lines. The IC₅₀ value of the extract on HeLa cells was 782.25 µg/ml and on B16F10 cells it was 841.84 µg/ml (Gore et al., 2014). Silver nanoparticles (AgNPs) with alcoholic *B. eriantha* DC plant extract inhibited cell growth of MCF7 cancer cell lines by 27.34% (Chavan et al., 2020).

19.3.2.2 Antibacterial Activity

Silver and iron nanoparticles with alcoholic *B. eriantha* plant extract were screened by Chavan et al. (2020) for the antibacterial activity. The ZI was 14.12 ± 1.52 and 12.45 ± 0.52 against *Bacillus subtilis*, 11.20 ± 1.15 and 10.12 ± 1.02 against *Bacillus cereus*, 16.17 ± 2.08 and 13.06 ± 0.57 against *Staphylococcus aureus* and 15.24 ± 1.52 and 11.55 ± 1.18 against *Escherichia coli* with the silver and iron nanoparticles, respectively (Chavan et al., 2020). Essential oil showed antibacterial activity against *Streptococcus pyogenes* and *Staphylococcus epidermidis* with lowest minimum inhibitory concentration (MIC) and minimum bactericidal concentrations (MBC) values of 0.09% and 1.56% and 0.39% and 6.25% respectively (Pednekar et al., 2012). Another study was undertaken to evaluate the antibacterial activity of *B. eriantha*, which showed MIC value for *Bacillus subtilis* and *Staphylococcus aureus* as 5.25 mg/ml each, for *Escherichia coli* as 2.12 mg/ml and for *Salmonella typhi* the MIC value was 4.12 mg/ml. MBC values for *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi* were recorded as 10.5 mg/ml, 11.5 mg/ml, 3.5 mg/ml and 3.5 mg/ml, respectively (Dhande et al., 2015).

19.3.2.3 Anti-Diabetic Activity

Oral administration of *B. eriantha* DC at doses of 250, 500 mg/kg for 21 days to streptozotocin (STZ) induced diabetic rats, showed anti-hyperglycemic effects and restored biochemical parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and γ -glutamyl transpeptidase (γ -GT) to near the normal levels. Hence, it was demonstrated that the extract not only reduces the blood glucose levels but also alleviates the liver and renal damage associated with STZ induced diabetes in rats (Singh et al., 2011).

19.4 CONCLUSION

It is evident from the available data that the two species of *Blumea*, namely *B. lacera* and *B. eriantha* are immensely significant, making them potential candidates for further research by the application of various technological advances for the use of phytochemicals present in these plants. The current knowledge base will provide an impetus for future research in order to

achieve profitable exploitation of *B. lacera* and *B. eriantha* for advancement in the use of the phytochemicals for medicinal use.

KEYWORDS

- against gastric cell lines
- alanine aminotransferase
- *Blumea lacera*
- *Blumea eriantha*
- minimum bactericidal concentrations
- minimum inhibitory concentration
- streptozotocin

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CHAPTER 20

Chemical Characterization and Pharmacology of *Magnolia champaca* (L.) Baill. ex Pierre

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20.1 INTRODUCTION

Magnolia champaca (L.) Baill. ex Pierre (Syn.: *Michelia champaca* L.) known as “Joy perfume tree” belongs to the Magnoliaceae family. *M. champaca* is an evergreen plant native to tropical and subtropical areas of South and Southeast Asia which is commonly distributed in the Sub-Himalayan zones, Assam, Western Ghats, South India, Burma Yunnan, Indo-China, Siam, Malaya (Taprial, 2015). It is cultivated in Asian countries. *M. champaca* as crude material for medicinal and aroma products has high economic value. Oil could be extracted from the flowers and used for the production of perfumes, cosmetics, and hair oil. The whole plant was utilized in conventional medicine for the treatment of a wide range of diseases, including metabolic and infectious disorders (Panneerselvam et al., 2016; Dhandapani et al., 2017; Sinha and Varma, 2016).

20.2 BIOACTIVES

Previous phytochemical investigations have confirmed the presence of tannins, glycosides, alkaloids, sesquiterpene lactones, saponins, steroids, flavonoids, anthraquinones, coumarins, phlobatannins, and reducing sugars

in *M. champaca* (Manhas and Dahiya, 2017; Vijayanand and Thomas, 2016; Geetha et al., 2011; Shejale and Yeligar, 2019b; Taprial, 2015). Chemical compositions of volatile essential oils prepared by using various solvents and different extraction methods were investigated by GC-MS, GC-FID analysis. Monoterpene and sesquiterpene hydrocarbons were found to be the major compounds of flower essential oil (Kaiser et al., 1991; Rout et al., 2006, 2011; Báez et al., 2012; Ananthi and Chitra, 2013a; Liu and Wang, 2008). Fractionation and identification of chemical constituents present in leaf volatile oil-based on seasonal changes have been reported by Lago et al. (2009).

The presence of gallic acid and β -sitosterol in *M. champaca* leaves and stem bark were identified by HPTLC analysis (Ahmad et al., 2011c, 2012). HPTLC studies evidenced the presence of phenolic acids and flavonoids in *M. champaca* flowers (Ananthi and Anuradha, 2015). Bioactive sesquiterpene lactones, namely parthenolide and costunolide were isolated from *M. champaca* stem bark (Hoffmann et al., 1977). The presence of quercetin in *M. champaca* flowers were first reported by Kapoor et al. (2004). An oxoaporphine alkaloid Liriodenine, topoisomerase I inhibitor was isolated from *M. champaca* bark (Figures 20.1 and 20.2) (Zuhrotun et al., 2016).

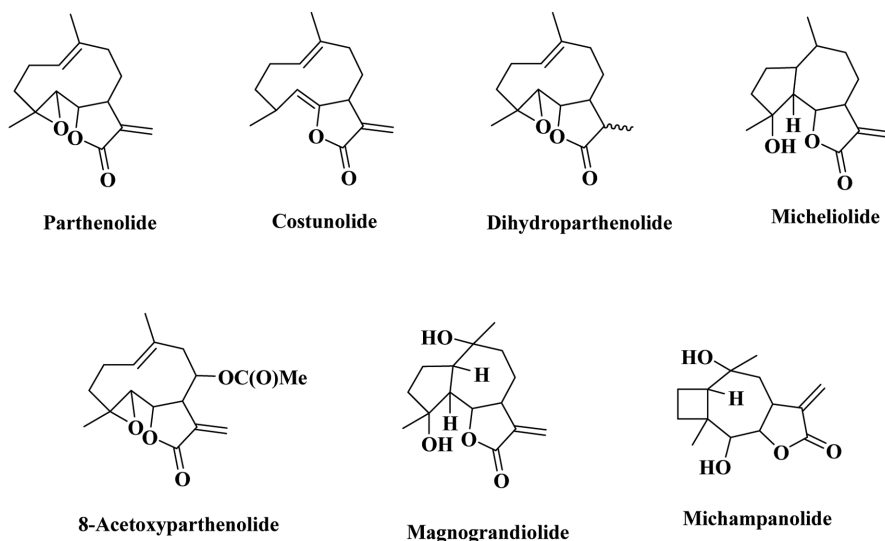


FIGURE 20.1 Sesquiterpene lactones isolated from *Magnolia champaca* (Govindachari et al., 1965; Jacobsson et al., 1995).

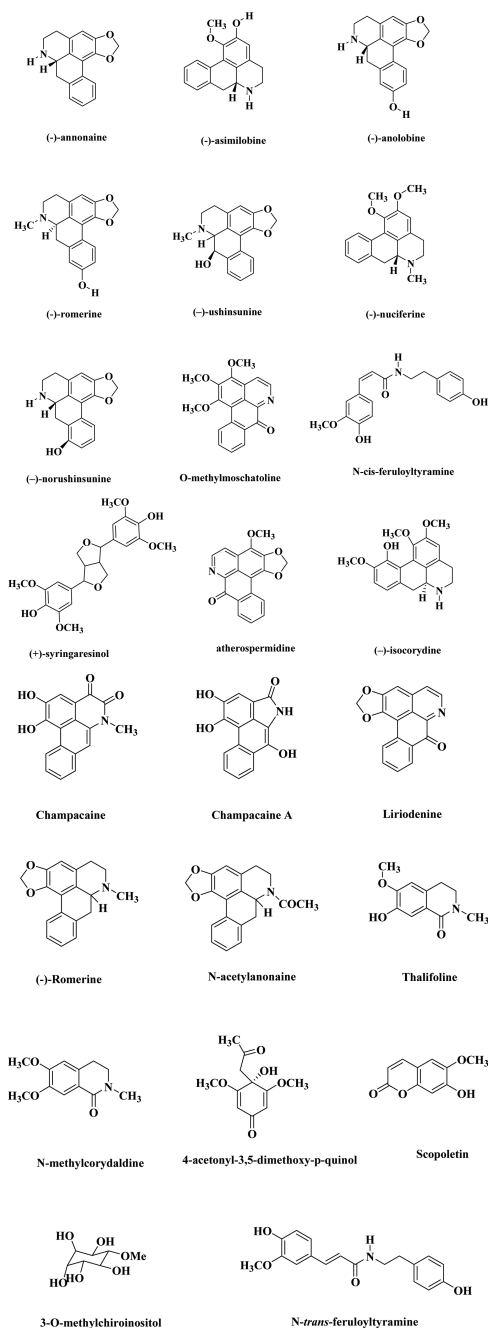


FIGURE 20.2 Compounds isolated from *Magnolia champaca* (Huang et al., 2014; Khan et al., 2002; Lin et al., 2018; Liu et al., 2020; Takahashi et al., 2015; Yeh et al., 2011).

20.3 PHARMACOLOGY

20.3.1 Antioxidant Activity

In vitro antioxidant efficacy of methanol extract of *M. champaca* flowers were evaluated by various methods and shown significant activity in all the assays (Ananthi and Chitra, 2013b). Another study reported the *in vitro* antioxidant efficacy of different solvent fractions of *M. champaca* stem bark methanol extract. Chloroform and ethyl acetate (EtOAc) fraction showed good antioxidant potential compared to other fractions (Hasan et al., 2020). Radical scavenging nature of *M. champaca* flower extract in different solvents was evaluated by Kumar et al. (2011a). Antioxidant properties of *M. champaca* seeds, flowers, and leaves were assessed by DPPH radical scavenging method. Chemical composition of the extracts were evaluated. All the extracts exhibited significant radical scavenging activity (Wei et al., 2011). *M. champaca* fruit extract in chloroform solvent exhibit good radical scavenging property (Vijayanand and Thomas, 2016). Jaishree et al. (2011) reported the comparison study of antioxidant activity of *M. champaca* methanol extract obtained by microwave and Soxhlet assisted extraction methods.

20.3.2 Antimicrobial Activity

Preliminary antimicrobial activity of *M. champaca* flowers were screened against gram-positive and gram-negative microorganisms by plate dispersion technique and exhibit significant activity (Lavanya et al., 2017; Kumar et al., 2011a). Antibacterial property of crude extracts of *M. champaca* flowers in hexane, ethyl acetate solvents, and isolated compounds were evaluated against four different bacterial strains. The crude extract showed significant results compared to pure compounds (Parimi and Kolli, 2012). *M. champaca* leaf, seed, root, and stem bark extract in methanol and its solvent fractions and pure compound Liriodenine were tested for antimicrobial activity. Solvent fractions exhibit considerable activity compared to crude extract against all the tested bacteria and protozoan (Khan et al., 2002). *In vitro* antimicrobial efficacy of *M. champaca* leaf and stem extracts in different solvents were screened against nine bacteria and two fungi. Hexane and chloroform extracts shown potent inhibition against tested microbes (Manhas and Dahiya, 2017). 70% methanolic extract of *M. champaca* seed and flowers significantly inhibit

the growth of selected bacterial strains (Wei et al., 2011). Marotrao (2015) reported the antimicrobial nature of essential oil from *M. champaca* flowers.

20.3.3 Anti-Inflammatory Activity

In vitro anti-inflammatory activity of methanol extract of *M. champaca* flower and ethanol extract of *M. champaca* leaves were evaluated by using human red blood cell membrane stabilization method. The extract exhibited membrane stabilization effect of 57.4% at the concentration of 300 µg/ml (Ananthi and Chitra, 2013c; Ananthi et al., 2016). Methanol extract of *M. champaca* flowers were found to reduce inflammation in cotton pellet granuloma in rodents (Vimala et al., 1997). Anti-inflammation activity through antioxidant property of a compound ferulic acid isolated from *M. champaca* was evaluated (Deepa et al., 2019). Gowda et al. (2014) reported the injury recuperating potential of 95% ethanol extract of *M. champaca* flowers in streptomycin incited diabetic rat models. Results showed that oral administration of ethanol extract enhance the wound healing process. Another study examined the wound healing profile of *M. champaca* in various wound models in rats and its effect on Dexamethasone suppressed wound healing (Dwajani et al., 2009).

20.3.4 Anti-Diabetic Activity

Anti-hyperglycemic activity of petroleum ether, chloroform, acetone, ethanol, aqueous extracts of *M. champaca* flower buds were evaluated in glucose overloaded hyperglycemic rat models. Results showed that the ethanol extract has a significant hypoglycemic effect (Jarald et al., 2008).

20.3.5 Anticancer Activity

In-vitro cytotoxicity of *M. champaca* flowers extract in methanol solvent were screened on EAC cell line by trypan blue dye exclusion method and MTT assay. *M. champaca* extracts showed potent concentration dependent anti-cancer activity (Ananthi et al., 2014b). Another study reports the anti-cancer activity of *M. champaca* flower and seed extract against MCF-7 cell lines (Wei et al., 2011). Methylene chloride extract of *M. champaca* bark exhibit remarkable cytotoxicity against human amelanotic melanoma (C32) and HeLa cell lines (Atjanasuppat et al., 2009).

20.3.6 Anti-Ulcer Activity

Anti-ulcer property of *M. champaca* flower and leaves was assessed against aspirin induced gastric ulceration in animal models. Evaluation of anti-ulcer potential is based on reducing the volume of gastric juice, total acidity value, ulcer index and more pH. All the tested extract possess anti-ulcer activity and flower aqueous extract showed remarkable activity than all other extracts (Kumar et al., 2011b).

20.3.7 Antitubercular Activity

Shejale and Yeligar (2019a) reported the growth inhibition potential of crude extract of *M. champaca* flower and three compounds against *Mycobacterium tuberculosis* was screened by using Alamar blue susceptibility test. Pure compounds have higher anti-tubercular activity in comparison with the extract.

20.3.8 Leishmanicidal Activity

In vitro leishmanicidal property of methanol extract prepared from *M. champaca* timbers along with other 74 plant timber extracts were evaluated by Takahashi et al. (2004). Results revealed that *M. champaca* have potent leishmanicidal property.

20.3.9 Helmintholytic Activity

Activity of methanol and water extracts of *M. champaca* against worm infections were investigated based monitoring time required for the occurrence of paralysis and death of the earthworms. Both the extracts showed dose dependent activity (Dama et al., 2011).

20.3.10 Antihyperlipidemic Activity

In a rat model of hyperlipidemia induced by Triton WR 1339, the lipid-lowering activity of 70% methanol extract from *M. champaca* was studied. By reducing serum cholesterol, triglycerides, low-density lipoprotein (LDL) and increasing high-density lipoprotein levels, it was found that methanol extract has the potential to lower blood lipids (Ananthi et al., 2014a).

20.3.11 Anti-Arthritic Activity

The anti-arthritic activity of *M. champaca* leaves in ethanol solvent was evaluated against Freund's adjuvant induced arthritis (AIA) in rats. The results showed that at a dose of 500 mg/kg body weight, ethanol extract can protect rats from CFA-induced primary and secondary arthritis damage, weight changes, and hematological disorders (Dhanalakshmi et al., 2012).

20.3.12 Diuretic Activity

The diuretic activity of water extracts of *M. champaca* stem bark and leaves were evaluated in Swiss albino Wistar rats. Aqueous stem bark extract showed better diuretic activity. Both aqueous extracts displayed good diuretic activity at higher doses (Ahmad et al., 2011b).

20.3.13 Procognitive Effect

Memory enhancing effects of *M. champaca* leaf extract in hexane solvent were investigated in adult Swiss albino Wistar mice models. The extracts showed dose dependent nootropic potential (Ahmad et al., 2011a).

20.3.14 Antifertility Effect

Taprial et al. (2013) evaluated the *in vivo* anti-fertility effects of hydroalcoholic extracts of *M. champaca* leaves. Leaf extract showed significant anti-fertility effect, which may be due to the inhibition of implantation and estrogenic effects.

20.3.15 Anti-Malarial Activity

Two sesquiterpene lactones, namely parthenolide and costunolide diepoxide isolated from *M. champaca* flowers exhibit potent schizonticidal antimalarial activity in tested rodent models. These results were further confirmed by *in silico* and molecular docking studies, which explains the mechanism probable binding orientation and target site of the molecules (Mehrotra et al., 2017).

20.3.16 Respiration and Cardioprotective Effects

Saqib et al. (2018) reported the effect of *M. champaca* extracts in ethanol solvent and its mechanism of action in gastrointestinal, respiratory, and cardiovascular disorders.

20.3.17 Molecular Docking Studies

Dash et al. (2020) evaluated the capability of *M. champaca* phytochemicals for cough treatment by molecular docking method. Docking studies revealed that Magnoflorine effectively inhibit the reproduction of microorganisms by interrupting their life cycle. Another study reported the ability of *M. champaca* phytochemicals for the treatment of skin disease caused by *Staphylococcus aureus*. Molecular docking studies explained that Magnoflorine effectively arrests the growth of microorganism by interrupting their life cycle (Bhat-tacharyay et al., 2020).

KEYWORDS

- *Michelia champaca*
- hydrocarbons
- *Magnolia champaca*
- microorganisms
- monoterpene
- sesquiterpene

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CHAPTER 21

Biomolecules and Therapeutics of *Plantago ovata* Forssk.

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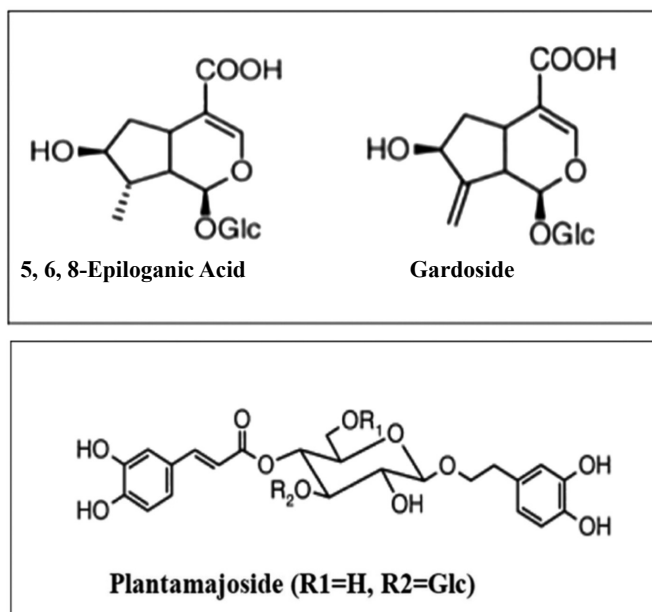
21.1 INTRODUCTION

Plantago ovata is commonly known as Psyllium, whose seeds are employed commercially for mucilage production. *P. ovata* is commonly known as Isabgul, Isparjah, Ispagul, Ishakol, Aspsgol, Eshopgol, Ispoghul, Isphaghul, Ispagala, Bartang, Isabagolu, Ghora jeeru, Umto, Ispagola Urthamujirum, Ishapupukol, vittulu, Isphagula, Bazrequatuna, Blond psyllium, Bazrekatima, and Isparzah. *P. ovata*, is a member of the Plantaginaceae family and this genus consisted of over 200 species. It is a woolly annual herb of the height of 30–45 cm, having a small terete stem, whorled with narrowly linear leaves. Spikes are ovoid in shape and bear flower around 45–70 in number, and capsular fruits are ellipsoid, obtuse, membranous, glabrous with ovoid, boat-shaped seeds. Plantago seeds outer seed coat possesses up to 10–30% hydrocolloid that can be upon further hydrolysis separated into neutral and acidic polysaccharides like L-rhamnose, D-galactose, L-arabinose, D-xylose, and D-galacturonic acid. The suspension of *Plantago* gum is thixotropic in nature while its mucilage has potent disintegrant character. Plantago seeds husk is in the form of membranous rosy-white layer, which is utilized as laxative, in constipation, dysentery, and chronic diarrhea as cent-percent herbal product (soluble fiber and forms gel in water) @7.5 g

dose usually (Fischer et al., 2004; Guo et al., 2008). Draksienė et al. (2019) evaluated super-disintegrate power of psyllium husk powder for making of orodispersible tablets used extensively in the pharmaceutical industry while Madgulkar et al. (2015) reported after characterization of *Psyllium* that it stimulates peristalsis in the gut and its modification by cross-linking of polysaccharide made it a medicinal excipient with many uses. Hussain et al. (2016) reported about its antiamebic, anticancer, antinociceptive properties and antiseptic property. Salient clinical assessment exhibited that the herbal medicine or husk of *P. ovata* consumed as laxative and recovered glucose homeostasis, lipoproteins, lipid profile, water secretion, urea, sodium chloride levels but its inner seed endospore contains protein or allergens which upon consumption alters physiology, metabolism, swelling in lip, throat, and asthma by inhalation of powder as psyllium contains antigen-specific IgE (Agha et al., 2016). Patel et al. (2020) confirmed after metabolomics of *P. ovata* that it contains PUFA, such as LA, ALA, GLA, and AA which makes it a suitable candidate for manufacturing of biomedical and nutraceuticals future use. *P. ovata* have multifarious applications in non-gastrological and gastrological diseases like diarrhea, diabetes, constipation, IBS, Crohn's disease (CD), regular lipid or glucose level and due to low cost, hydrophobicity, biocompatibility, biodegradability, nontoxic, bio-renewability, heavy metal ion scavenging or wastewater remediation properties made it excellent candidate plant (Gonçalves and Romano, 2019).

21.2 BIOACTIVES

Plantago seeds outer seed coat possess up to 10–30% hydrocolloid that can be upon further hydrolysis separated into neutral and acidic polysaccharides like L-rhamnose, D-galactose, L-arabinose, D-xylose, and D-galacturonic acid, tannin, aucubin glycoside (iridoid), sterols, sugars, fixed oils, and protein. Its mucilage consists of arabinose, galacturonic acid and xylose, with rhamnose and galactose. *Plantago* species contains a vivid bioactive secondary metabolite, i.e., iridoids, polysaccharides, sterols, alkaloids, phenols, cumatines, epiloganic acid, plantamajoside, and gardoside. Beside mucilage, its seed possess tannin, aucubin, and semi drying fatty oil @ 5% (yellow colored). Amino acids like alanine, valine, tyrosin, lysine, cysteine, glycine, leucine, and glutamic acid present and fatty acids constituent obtained were linolenic, linoleic, oleic, palmitic, stearic, and lignoceric oil. Starch yielded from dehusked seed (Sarfraj et al., 2017).



21.3 PHARMACOLOGICAL CHARACTERISTICS

21.3.1 Mucilage

P. ovata mucilage content made it pharmaceutical excipients involved film formation, disintegrating, binding, suspending, thicker, and emulsifying qualities due to low cost and vegetative origin in various granules and tablet formation (Basavaraj et al., 2012; Sarfraz et al., 2017) in pharmaceutical industry. Mucilage obtained from psyllium consisted of (xylose 74.6% and arabinose 22.6%) which has nontoxic nature and possess a group of biological activity in combination of chemical, physical, and mechanical properties that made it useful biomaterial for pharmaceutical industry (Kumar et al., 2017). Investigation was to formulate the drug with *P. ovata* mucilage (natural super disintegrant) optimized with rapimelts (orodispersal tablets used to reduce cold symptoms and allergy) consisting metoclopramide HCl and such prepared tablet with *P. ovata* mucilage upon dissolution were capable of releasing up to 90% drug within 15 minutes with an appropriate combination of excipients which is superior than other conventional technique (Tripathi and Gautam, 2019).

21.3.2 Disintegrant

Superdisintegrants are compounds which upon addition to the tablets makes, splitting of thick mass into small particles, to facilitate drug dissolution and discharge of active component during it approaches to the surroundings fluid. *P. ovata* is used as effective super disintegrant agents or fast disintegrating tablets (FDT's) that are considered as novel type of tablets which disintegrate/disperse or dissolve easily in saliva and consumed by geriatrics, pediatrics, mentally disabled and bed ridden patients who have suffered from dysphagia, coughing, nausea, allergy, and motion sickness. Rajamanickam et al. (2010) used 5% w/w *P. ovata* concentration of (seed, mucilage, and husk powder) for super disintegrant tablet synthesis and recorded 31, 35, and 38 s disintegration time. *P. ovata* formulated tablets exhibits little disintegration time rather than sodium starch glycolate made tablets due to its mucilage or high swelling index (Sarfranz et al., 2017).

21.3.3 Suspending Agent

Validation of *P. ovata* as suspending agent evaluated by ispaghula mucilage powder suspension and compared with the nimesulide (standard drug) of market (Rajamanickam et al., 2010). Researches revealed that psyllium polysaccharide (PPS) mucilage possess remarkable potential of suspending agent among various formulations (Sarfranz et al., 2017).

21.4 HEALTH BENEFITS OR PHARMACOLOGICAL ROLE OF PLANTAGO OVATA

There are multifaceted health benefits associated with *P. ovata* evident in the control of diarrhea, constipation, irritable bowel syndrome (IBS), hypercholesterolemia, and diabetes (Table 21.1). Some are discussed in subsections.

21.4.1 Wound Healing Properties

Ethanollic extract of *P. ovata* seeds exhibit wound healing tendency (Singh, 2007) therefore its extract (10% w/w in petroleum jelly base) was used as an ointment to treat wound immediately with minimum pain and irritation to albino rats and concluded that ethanollic extract helped in wound contraction

significantly with increased wound healing. Westerhof et al. (2001) studied *in vivo* and *in vitro* and reported that mucopolysaccharides obtained from psyllium (*P. ovata*) husk have good properties for cleansing and healing of wound (limiting scar) significantly. Patil et al. (2011) used psyllium for wound dressing material with povidone-iodine and reported that such film not only have proper elasticity (80.27–116.24%), optimum swelling index (167 to 191% w/w), permissible tensile strengths (8.33–22.13 N/mm²) with good water vapor transmission but also exhibit anti-microbial properties.

TABLE 21.1 Uses of *Plantago ovata* for Human Health Disease

SL. No.	Disease	References
1.	Wound healing	Westerhof et al. (2001); Singh (2007); Patil et al. (2011)
2.	Constipation	McRorie et al. (1998); Siavash et al. (2007); Mehmood et al. (2011), Majumdar et al. (2013)
3.	Diarrhea	Washington et al. (1998); Thompson et al. (1999); Mehmood et al. (2011), Rachlis et al. (2005),
4.	Irritable bowel syndrome	Vejdani et al. (2006); Ford et al. (2008); Hosseini et al. (2015); Sarfraz et al. (2017)
5.	Ulcerative colitis	Fernandez-Banares et al. (1999); Hallert et al. (1991); Anonymous (2002); Krammer et al. (2005)
6.	Anti-inflammatory potential	Pylkas et al. (2005); Deters et al. (2005); Sarfaraz et al. (2017); Patel et al. (2020)
7.	Hypercholesterolemia	Anderson et al. (2000), Van Rosendaal et al. (2004); Garcia et al. (2009); Sola et al. (2007)
8.	Hypertension	Cicero et al. (2007, 2010)
9.	Diabetes	Sierra et al. (2001); Ziai et al. (2005); Bokaeiam et al. (2015); Agha et al. (2016)
10.	Hemorrhoids	Perez-Miranda et al. (1996); Kecmanovic et al. (2006); Haddadian et al. (2014)
11.	Anti-amoebic activity	Zaman et al. (2002)
12.	Obesity	Brum et al. (2016)
13.	Celiac disease	Cappa et al. (2013)
14.	Cancer treatment	Willson (1989); Lien et al. (2003); Singh and Bala (2014); Hasheminasab et al. (2020)

21.4.2 Anti-Diarrheal and Anti-Constipation Activity

Researches upon antidiarrheal and anti-constipating potential of *P. ovata* was explored by McRorie et al. (1998), Mehmood et al. (2011), Quitadamo

et al. (2012). They used crude extract of *P. ovata* to exert laxative role under muscarinic, 5-HT receptor-activated mice @ 100–300 mg/kg dose while at higher dose @ 500–1000 mg/kg dose exhibit gut inhibitory role in treated mice via activation of NO cGMP (cyclic guanosine monophosphate) pathway and calcium ion channel blockage. Psyllium crude extract in the 10 mg/ml treatment in Guinea pig's ileum exhibited efficient anti-constipation activity via stimulation of muscarinic serotonin receptors. Similar results were obtained in treated rabbit jejunum. Psyllium enhanced stool softening and the bowel movement frequency rather than docusate (stool softener), thus potential tool for relief from chronic constipation (Siavash et al., 2007; Majumdar et al., 2013) and hemorrhoids bleeding (Haddadian et al., 2014).

21.4.3 Hypocholesterolemic Activity

Ispaghula husk (psyllium) addition to the hypercholesterolemia patient diet led to significant recovery (Sprecher et al., 1993; Uehleke et al., 2008; Van Rosendaal et al., 2004). *P. ovata* husk had considerable potential for reduction in total cholesterol and LDL cholesterol under-treated humans and animals via increased hydroxylase activity with bile juice synthesis (Anderson et al., 2000; Ribas et al., 2015) stimulation. Sharma and Bhattacharya (2009) found that Isabgol increases the breakdown and decreases the absorption of bad cholesterol while Moreyra et al. (2005) found that psyllium in combination with the drug simvastatin, improves cholesterol reduction to treat hypercholesterolemia. Garcia et al. (2009) reported that hypercholesterolemic patients treated with ispaghula (7 g/day for 6 months) containing diet leading to the 8.7% depletion in LDL cholesterol level and 7.7–8.9% of total cholesterol level. Verma and Mogra (2015) reported that psyllium (15 g/day) administration for six weeks in postmenopausal women, remarkably reduced the total cholesterol amount up to 5.2% rather than 1.3% in premenopausal women. Administration of psyllium @14 g/day for (8 weeks) to hypercholesterolemia patients, leading to the reduction in the plasma LDL-cholesterol, insulin, triglycerides, systolic blood pressure (SBP) and apolipoprotein B-100 significantly (Sola et al., 2007).

21.4.4 Anti-Inflammatory Activity

Anti-inflammatory potential evaluation of *Psyllium* in HLA-B27 transgenic rats, concluded that psyllium reduced leukotriene B₄, NO, and TNF

inflammation mediators which involved in intestinal inflammation (Siavash et al., 2007; Deters et al., 2005). It contains plenty of antioxidants and scavenging properties which control cell damage or wound healing and promotes regeneration of tissue with boosting immune system (Sarfaraz et al., 2017; Patel et al., 2020). Anaerobic fermentation of *Psyllium* in the gut produces various types of fatty acids which attributed to the antioxidant and anti-inflammatory activity (Pylkas et al., 2005). Psyllium based hydrogel with Aspirin drug is a potential anti-inflammatory drug reported by (Rosu and Bratu, 2014).

21.4.5 Hypoglycemic Activity or Diabetes

Dietary fibers from psyllium have been used as ingredients in food to regulate glucose amount in diabetic patients via reducing serum lipid levels (Abdelaaty et al., 2012; Siavash et al., 2007). Diabetes mellitus (type 2 DM) patient exert significant absorption of carbohydrates during psyllium consumption (Clark et al., 2006; Cicero et al., 2010; Sierra et al., 2001; Siavash et al., 2007). *P. ovata* husk (aqueous extract) which not only inhibited the postprandial blood glucose but also decelerate the absorption in small intestine without stimulating sucrose influx in large intestine therefore suggestive its application in diabetes therapy (Sarfaraz et al., 2017; Ricklefs-Johnson et al., 2017). Bokaeiam et al. (2015) investigated those patients with type II diabetes treated with natural soluble fiber supplement psyllium (*P. ovata*) @ 5.1 g bid., to reduce glucose at best level. The values of change in HDL cholesterol were 4.16 to 3.05%, LDL-cholesterol were 2.78 to 22.8%; and the triglycerides were dropped from 8.49 to 19.54% in Psyllium treated children (Agha et al., 2016). The effect of psyllium husk was studied in 34 men with type 2 diabetes and hypercholesterolemia given either placebo or 5.1 g psyllium twice daily for eight weeks. Ziai et al. (2005) evaluated that ispaghula @ 5.1 g per person before breakfast and dinner in type II diabetic patient is significantly correct glycemic index and also reported that psyllium in combination with the drug glibenclamide, contributed hypoglycemic effect to treat diabetes hypertension is also regulated with the psyllium rich diet consumption (Cicero et al., 2007, 2010). Total cholesterol was lower by 8.9% and LDL by 1.0%. In addition, psyllium feeding not only caused viscosity in the intestine to prevent excess absorption of neutral steroids and bile acids but also reduced the postprandial rise of glucose significantly (Anderson et al., 1999).

21.4.6 Influence on Autonomic Gastrointestinal Disorder

Inflammatory bowel disease (IBD) was commonly treated with common medicinal *P. ovata* plant. Its seed consumption decreased the colon inflammatory barriers by producing the short-chain fatty acids while their alcoholic extract illustrates cholinergic activity (Bijkerk et al., 2004; Ford et al., 2008; Vejdani et al., 2006; Tewari et al., 2014; Moayyedi et al., 2014). Isabgol helps to control obesity as it is rich in fiber and helps to clean the colon and remove toxins from the body responsible for obesity due to its Guru (heavy) nature. Anticholinergic drugs induced autonomic GI dysfunction related to Parkinson disease, treated with the Psyllium husk, thus *P. ovata* husk ameliorate the levodopa pharmacokinetics via dyskinesia delaying (Sarfraz et al., 2017). It also adds a layer of protective lining to the inner side of the stomach that helps in reducing hyperacidity due to its Sita (cold) nature. Psyllium seeds were found to be effective in patients for the treatment of gastroesophageal reflux disease (Hosseini et al., 2015).

21.4.7 Hemorrhoids Treatment

Perez-Miranda et al. (1996) evaluated the effect of fiber supplements, including *P. ovata* on internal bleeding hemorrhoids. Around 50 persons with internal bleeding hemorrhoids were given either a placebo of B vitamins or 11.6 grams of Metamucil® daily for 40 days. Individuals in the psyllium group had significant improvement in reduction of bleeding and a dramatic reduction. Bleeding was stopped after treatment in the psyllium group, while those in the control group experienced no difference. Kecmanovic et al. (2006) determined the role of *P. ovata* after open hemorrhoidectomy to minimizing the post-operative pain and tenesmus in patients into two sets of randomized trial of 49 patients in each group, where one group is treated with 3.26 g dose of *P. ovata* (twice a day) while another group is treated with glycerin oil only and concluded that significant relieve in pain, tenesmus rate and discharged early from hospital rather second group. Haddadian et al. (2014), reported that *P. ovata* is used as a laxative to treat duodenal ulcer or hemorrhoids stool softening.

21.4.8 Ulcerative Colitis

CD or ulcerative colitis is a chronic, inflammatory disease of the digestive tract which occur recurrently. The intestinal tract consisted of (a) esophagus or food pipe (b) stomach, for churning and digestion of food (c) the long and

small intestine or bowel, for absorption of nutrients, vitamins, and calories (d) colon and rectum, for absorption of water and storage of stool. An important primary site for CD, are the ileum (end part of small bowel) and the colon. During CD small, inflammatory site appeared initially which later converted into large ulcerated, thickened bowel wall, finally converted to the obstructed or narrowed bowel and treated by surgery only. Dietary fiber or psyllium found to be beneficial in regulating human ulcerative colitis, via increased production of short-chain fatty acids (SCFA) in the lumen, which is involved in the inhibition of pro-inflammatory mediators production synergistically (Hallert et al., 1991; Rodriguez-Cabezas et al., 2003). *P. ovata* seed administration significantly increased in fecal butyrate levels after colonic fermentation, which is effective in active distal ulcerative colitis treatment. Reports stated after randomized, open multi-center trial of ulcerative colitis, patients, that psyllium seed intake (10 grams twice daily) is equally effective as drug 'mesalamine' to remission maintenance by elevated butyric acid level with psyllium products (Fernandez-Banares, 1999; Anonymous, 2002). HLA-B2712 induced colonic damage was ameliorated with Psyllium fiber dietary supplementation (Krammer et al., 2005) in transgenic rats.

21.4.9 Diarrhea Treatment

Normally looseness of stool in diarrhea is measured with ratio of fecal water excretion, while Psyllium decreases the liquid stools amount with increased in the amount of normal stool. Gut infected by ETEC (enterotoxigenic *E. coli*) triggered secretory diarrhea by stimulating electrolytes and fluid secretions. Such type of ETEC induced diarrhea were ameliorated with the Psyllium uptake in piglet jejunum via calcium-mediated secretory responses (Hayden et al., 1998). Quitzau et al. (1988) and Thompson et al. (1999) tested fecal consistency with psyllium treated and control experiments and reported that psyllium in combination with calcium will be the probable cheap and good substitute for chronic diarrhea treatments contrarily psyllium also increases constipation with increasing stool weight (Kumar et al., 1987). Washington et al. (1998) reported that psyllium is good enough in the control of lactose-induced diarrhea, via delaying empty gastric and fermented gaseous product formation with lowering colon transit acceleration while Rachlis et al. (2005) investigated the role of *P. ovata* in the regulation of protease inhibitors (PIs) induced diarrhea effectively.

21.4.10 Treatment of Metabolic Disorders

P. ovata husk @ 3.5% in diet prevent dyslipidemia, hypertension, endothelial dysfunction and obesity (Brum et al., 2016; Sarfraz et al., 2017) and psyllium fiber supplements remarkably control BP, cardiovascular disease (CVD) risk as it contains acid and neutral polysaccharides like galacturonic acid with an adequate soluble/insoluble fiber attributed towards anti-obesity properties (Verma and Mogra, 2015). Galisteo et al. (2010), investigated the role of psyllium husk rich diet to the adult obese Zucker rats, suffering from hyperleptamia, hyperinsuemia, hyperlipidoma, increased body weight, increased TNF- α , poor adiponectin release from adipose tissue and concluded that due to its low hepatic content properties via cAMP kinase enzyme in liver made it potent product which can corrected various metabolic disorders.

21.4.11 Anti-Amoebic Activity

Amoebiasis caused by the pathogenic strain *Entamoeba histolytica* (present in sewage), responsible for the mortality of many people every year around the world by consuming contaminated water and food. Such bacterial population were inhibited with crude and petroleum extract of psyllium in the concentration of 0.1–1.0 mg/L and 1.0–10 mg/L, respectively, and amoebic dysentery were effectively controlled with the petroleum extract of psyllium (Zaman et al., 2002).

21.4.12 Treatment of Celiac Disease

Celiac disease is an autoimmune disorder usually occurred in genetically predisposed person, causing damage to the small intestine by gluten-rich diet. Hence psyllium is best substitute for gluten in different diet of celiac patients like wheat bread dough is modified with psyllium. Cappa et al. (2013) reported that such modified breads have low fat and energy and psyllium supplementation is significantly good due to its mixing, leavening, film formation, and water retention capabilities for making of gluten free dough's.

21.4.13 Use in Cancer

Sarfraz et al. (2017) reported the cytotoxic effect of *P. ovata* in different types of cancer. Colon cancer developed by bile acids which enhance the

multiplication of colon cells by chronic inflammation in the colon like ulcerative colitis. Dietary fibers mimic the risk of colon cancer by diluting bile acids and reducing transit time. Human epidemiology is correlated with high-fiber consumption in diet and low risk of colon cancer. Such fibers inhibit colon tumorigenesis by binding with carcinogens, potential toxins, bile juices, essential nutrients (minerals) and modulate microbial activity within the intestinal lumen. Psyllium uptake is associated with the production of SCFA (short-chain fatty acid), and its fermentation yielded *n*-butyrate which has antineoplastic property against human colon carcinoma cells. Both SCFA and *n*-butyrate controlled adenomas and colonic cancer or reverted cells from a neoplastic to a non-neoplastic phenotype (Kim et al., 1980; Robert-Andersen et al., 1987; Willson, 1989). Morita et al. (1998) deduced that psyllium enriched diet changed the fermentation site from cecum towards colon via increased *n*-butyrate amount in colon, regulated the risk of colon cancer. Lien et al. (2003) studied application of psyllium for wound healing, inflammation, and cancer since ancient times. Psyllium consumption raised the bulk of stool with deadly compounds deposits from the wall of the intestine which attributed to its colon cancer prevention capability (Singh et al., 2008; Singh and Bala, 2014) while Hasheminasab et al. (2020) tested psyllium-based compounds upon oral mucositis in patients with breast cancer in randomized trial and found its efficacy to manage such patients. Galvez et al. (2003) investigated the cytotoxic effect of psyllium against breast carcinoma cancer cell lines in humans. Singh and Bala (2014) reported that psyllium-based hydrogel with methotrexate drug is a potential anticancer drug.

21.4.14 Use for Appetite

Psyllium uptake influence appetite directly as psyllium seed @ 20 grams, three hours pre-meal followed with post-meal for consecutive three days increased the fullness feelings which in turns reduced the fat intake with their meals after one hour (reports from Anonymous, 2002) therefore mimic frequent eating.

21.4.15 Use for Nutraceutical

Psyllium fiber derived from *P. ovata* husk has excellent physiochemical, scavenging, antioxidative, antiproliferative properties attributed to its role as

best nutraceutical synthesis (Patel et al., 2016). Commercialized worldwide preparations are Fybogel, Ispagel, Isabgol, Metamucil, Naturolax, etc., manufactured with it.

21.4.16 Control of Acne and Pimples

Psyllium provides relief from common skin problems like acne or pimples. As per Ayurveda, an aggravation of Kapha leads to an enhanced sebum secretion and clogging of pores which ultimately results into the white and blackheads formation while Pitta accumulation caused inflamed red bumps with pus. External application of Isabgol paste helps to check excessive production of sebum and removes the clogging of pores. It also helps to reduce inflammation and gives soothing effects due to its *Sita* (cold) properties (Gupta et al., 2019).

21.4.17 Control Tooth Decay

Reddy et al. (2018) evaluated the antibacterial property of *P. ovata* leaves and seeds against *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Aggregatibacter actinomycetemcomitans* (periodontal pathogens) and against metalloproteinase-2 (MMP-2) and MMP-9 (inflammatory mediators) matrix and concluded that it is an effective substitute of conventional antibiotics used for tooth infections.

21.4.18 Limitations

Pharmaceutical industries, workers are more prone to allergic reactions particularly respiratory like asthma-related problems because of handling psyllium powder for bulk laxatives formulations and such reactions occurred due to inhalation or skin contact with dust containing psyllium (Freeman, 1994), therefore, Hoffman (2006) called it as bane for producer and boon for patients.

21.5 CONCLUSION

Appropriate techniques need to be developed to improve the traditional process of milling of seeds and to explore the possibilities of preparing newer

high valued commercial products out of the seeds and husk of the crop in the benefit of cultivators and plant-based industries (Tewari et al., 2014). It is an eco-friendly, effective, safe, economical wonder drug used for multifaceted disease treatment as an alternative to synthetic drugs.

KEYWORDS

- **cardiovascular disease**
- **Crohn's disease**
- **inflammatory bowel disease**
- ***Plantago ovata***
- **protease inhibitors**
- **psyllium polysaccharide**
- **short-chain fatty acids**

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CHAPTER 22

Phytochemistry and Pharmacology *Ipomoea mauritiana* Jacq.

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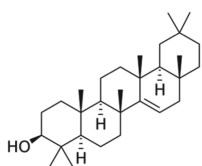
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22.1 INTRODUCTION

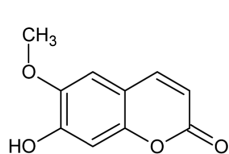
Ipomoea mauritiana, commonly known as Giant potato, is an ethno-medicinally important species belonging to the family Convolvulaceae and is used in many traditional systems of medicine like Ayurveda and Folk medicine. It is one of the source plants of ‘*Vidari*,’ an Ayurvedic drug which is a component of many Ayurvedic formulations including *Chyavanaprash* (Sivarajan and Balachandran, 1994). In India, Ayurvedic Pharmacopeia correlates *I. mauritiana* as *Kshiravidari* and is used as *Vidari* in many parts of the country. It is a branched perennial climber with large tuberous taproots and glabrous stems and branches; leaves palmately 5–7 lobed; flowers purple, in pedunculate corymbose axillary panicles; fruits ovoid, four-celled, and four-valved capsules, surrounded by enlarged fleshy sepals, seed clothed with many long tawny cottony hairs. The root tubers exude milky, sticky, latex, and exhibit annual rings when cut. This species is widely naturalized in tropical parts of the world (Warrier et al., 2007). The roots are sweet, cooling in action, appetizer, galactagogue, rejuvenating, stimulant, carminative, and tonic. It is also used in emaciation, enteric fever and spermatorrhea (Karthik et al., 2009; Udayan and Balachandran, 2009; Sulaiman et al., 2014).

22.2 BIOACTIVES

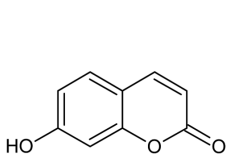
Chemical evaluation revealed the presence of various phytochemicals, including alkaloids, saponin, terpenoids, phenolics, flavonoids, and coumarins. Tuberous root contains taraxerol, taraxerol acetate, β -sitosterol, 7-O- β -Dglycopyranosyl, and caffeoyl glucose (Khan et al., 2009; Sulaiman et al., 2014; Alam et al., 2020). Coumarins such as 7-Hydroxy-6-methoxy coumarin, 7-Hydroxycoumarin, 5-methoxy-6,7-furanocoumarin, 5,7-dimethoxycoumarin and 6-Hydroxy-7-methoxy-4-phenylcoumarin have been reported from tuber root (Sulaiman et al., 2019).



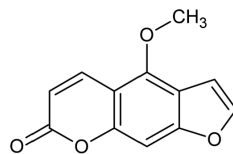
Taraxerol



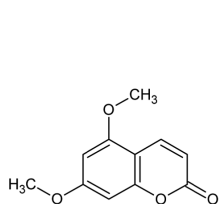
7-Hydroxy-6-methoxy coumarin



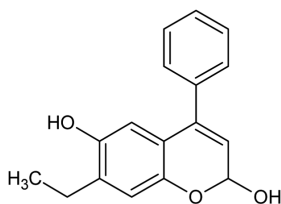
7-Hydroxycoumarin



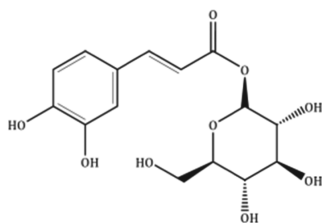
5-Methoxy-6,7-furanocoumarin



5,7-Dimethoxycoumarin



6-Hydroxy-7-methoxy-4-phenylcoumarin



Caffeoyl glucose

22.3 PHARMACOLOGY

22.3.1 Analgesic Activity

Methanolic extract of callus showed analgesic activity at the highest dose of 400 mg/ kg. The extract at doses of 50, 100, 200, and 400 mg per kg significantly reduced the number of writhing in mice by 23.3, 33.3, 43.3, and 53.3%, respectively (Islam et al., 2015).

22.3.2 Antibacterial Activity

Crude methanol extract of *I. mauritiana* showed prominent antibacterial activity against *Bacillus cereus* with mean zone of inhibition (ZI) ranging from 37 to 42 mm at a concentration of 400 µg /disc (Alam et al., 2020).

22.3.3 Antioxidant Activity

I. mauritiana methanol extract showed 72.28% DPPH radical scavenging at a concentration of 800 µg/mL. The extract showed an IC₅₀ value of 275.084 µg/mL (Alam et al., 2020). The study by Sulaiman et al. (2014) showed that compounds isolated from the tuberous root of *I. mauritiana* have significant radical scavenging activity with an IC₅₀ of 3.86 and 3.16 µg/mL.

22.3.4 Anti-Hyperglycemic Activity

In an oral glucose tolerance test conducted by Islam et al. (2015) with glucose-loaded mice, the callus extract of *I. mauritiana* at doses of 50, 100, 200 and 400 mg per kg significantly reduced blood glucose levels by 35.1, 42.5, 53.6, and 58.8% respectively.

22.3.5 Anti-Amnesic Activity

Aqueous tuber root extract of *I. mauritiana* at a dose of 100 and 200 mg/kg showed significant anti-amnesic activity against scopolamine-induced changes in step-through latency and working memory errors (Sulaiman et al., 2019).

22.3.6 Anti-Inflammatory Activity

Leaf extract showed anti-inflammatory activity in Carrageenan induced rat paw edema model (Pavan et al., 2017).

22.3.7 Hypocholesterolemic and Hypotriglyceridemic Activity

The tuber root powder of *I. mauritiana* showed a significant lowering of serum total cholesterol and triglycerides. The administration of tuber root powder also led to dose-dependent significant elevations in level of serum high-density lipoprotein (HDL)-cholesterol (Moushumi, 2010).

KEYWORDS

- bioactives
- Convolvulaceae
- high-density lipoprotein
- *Ipomoea mauritiana*
- pharmacology
- phytochemicals

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CHAPTER 23

A Review on Phytochemistry and Pharmacology of *Diospyros montana* Roxb.

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23.1 INTRODUCTION

Diospyros montana Roxb. belongs to the family Ebenaceae. It is a semi-evergreen tree, up to 8 m tall, often spiny. Leaves thick coriaceous, obovate or elliptic. Flowers white, unisexual, male flowers few, in short cymes, female flowers solitary, axillary, drooping on short pedicels. Fruit berry, globose, black when ripe. It grows in deciduous to dry evergreen forests up to 1200 m high in the hills in India, Sri Lanka, Nepal, Malaysia, and tropical Asia. Local names of this plant include Tumala (Sanskrit), Bangab (Bengali), Timbarao (Gujarati), Tendu (Hindi), Balagunike (Kannada), Gatugata, Eddayagata (Telugu), Timuru (Marathi), Vakkamai, and Vakkanatan (Tamil). *Diospyros* exhibits several pharmacological activities that include anticancer, cardioprotective, antihelmintic, insecticidal, antioxidant, antiprotozoal, antipyretic, cytotoxicity, neuroprotective, and hypnotic-sedative (Rauf et al., 2017). *Diospyros* genus is also very well-known for its uses in several traditional systems of medicines like Ayurveda, the Chinese Traditional system of Medicine, and the African folklore medicines (Kantamreddi et al., 2017). In the Indian traditional system of medicines like Ayurveda, several *Diospyros* species have been reported to be used medicinally to cure fever, diabetes, snake bite, diarrhea, biliousness, ulcer, etc. (Sinha et al., 2008). *D. montana* is traditionally claimed to form the treatment of various menstrual disorders and irregularities (Hossen et al., 2016). *D. montana* bark juice is filtered and dropped into the ear to treat ear infection,

leaking ear and puss in the ear (Harsha et al., 2002). The fruit of *D. montana* is used to treat hiccups, ulcers, urinary diseases, biliousness, dysentery, and bile tract stones (Utsunomiya et al., 2002). *D. montana* contains extensive varieties of structurally diverse secondary metabolites, which supports this traditional uses with its scientific pieces of evidence.

23.2 BIOACTIVE PHYTOCONSTITUENTS

Diospyros montana Roxb. is one of the therapeutically important plants, broadly distributed throughout the world. Out of 475, about 100 species of *Diospyros* are phytochemically explored, among which *D. montana* is one of the most potent species. Interestingly, all parts of the *D. montana* species have been investigated for the presence of an important class of phytochemicals are depicted in Table 23.1. Phytochemical profiling of *D. montana* has uncovered the presence of some imperious phytochemicals like steroids, naphthoquinones, triterpenes, polyphenols, and flavonoids. Various important phytoconstituents described include Lupane-type triterpenes, such as (a) Lupeol, Betulin, Betulinic acid (b) Allobetulin, Oxybetulin (Figure 23.1), Ursane-type triterpenoid metabolites such as Ursolic acid, Epiuvaol, and α -amyrin (Figure 23.2), Oleanane-type triterpenes Oleanolic acid, β -amyrin (Figure 23.3), the steroidal skeleton as (a) β -Sitosterol (b) Stigmasterol (Figure 23.4), 7-Methyljuglone (Figure 23.5), Monomeric, 1, 4-naphthoquinone derivatives as (a) Chromenone acid (b) Yerrinquinone (Figure 23.6), Naphthoquinones as (a) Diospyrin, (b) β -Dihydrodiospyrin, (c) Tetrahydrodiospyrin, (d) 8-Hydroxydiospyrin, (e) Cyclodiospyrin, (f) Isodiospyrin, (g) Biramentaceone, and (h) Mamegakinone (Figure 23.7) (Hazra et al., 2002; Rey et al., 1998; Sanyal et al., 2003; Dutta et al., 1972). Narayan et al. (1978) reported diospyrin, lupeol, and betulinic acid from the benzene extract of *D. montana* leaves. Tanaka et al. (2007) isolated and structurally elucidated five flavonol glycosides, two naphthalene dimer glycosides, and three new compounds from the leaves of *D. montana*. Hazra et al. (2007) depicted isolation of naphthoquinones and synthesized alkyl ethers diospyrin as a naphthoquinonoid derivative from the stem bark of *D. montana*. Pardhasaradhi and Nageswararao (1990) have reported oxygenated naphthoquinone carboxylate, yerrinquinone from fungal-infested wood of *D. montana* which was isolated by extracting with petrol (60–80°) and was confirmed by HNMR structural elucidation. Zhong et al. (1984) explored the bark/wood of 17 African species *Diospyros* for the presence of various triterpenes and naphthoquinones. Betulin, betulinic acid, and triterpenes lupeol were identified in all samples. Naphthoquinones were identified in 14 out of the 17 species, and the common

dimeric compounds found were diospyrin and iso-diospyrin. Pardhasaradhi and Nageswararao (1979) isolated a new reduced dimeric 7-methyljuglone from the fresh bark of *D. montana*, presented to be 3,7-dimethyl-5,6,7,8'-tetrahydro-1,5,5'-trihydroxy(2,2'-binaphthalenyl)-1,4,8'-trione. Lillie et al. (1976) reported novel diospyrin derivatives as dinaphthofuran 3, 5-O-cyclodiospyrin, 8-hydroxydiospyrin, 2- and 3-chlorodiospyrin, 3-chloro-2-hydroxydiospyrin, and Chromenone ester and acids from wood and bark of *D. montana*. Rauf et al. (1987) reported the isolation of 8-hydroxyoctadec-10 (Z)-enoic acid from the petrol extract of *D. montana* seeds. Kumar et al. (2011) studied the detection and quantitation of β -sitosterol in leaves, stem bark, roots, and seeds of *D. montana*. They have stated *D. montana* plant contains β -sitosterol that ranges from 200 to 1000 μgmL^{-1} which possess anticancer and adaptogenic properties. Hayek et al. (1989) reported the presence of betulin in the extract of bark, pulp, and roots of *D. montana*. Bacherikov et al. (2003) described the isolation of diospyrin and binaphthoquinoid derivatives from *D. montana*. Ravishankara et al. (2000) isolated and characterized diospyrin, a tumor inhibitory agent from the stem bark of *D. montana*. A sensitive high-performance thin-layer chromatography (HPTLC) method was established for the estimation of diospyrin. The method was validated for precision (intra- and inter-day), repeatability, and accuracy. The established HPTLC method was adopted for the estimation of diospyrin content of the stem bark of *D. montana* from different regions, which varied from 0.35 to 0.47% (w/w) in the samples. Sharma (2017) reported the isolation and characterization of diospyrin ester derivative diospyrin-2-(2-epoxy-3-methyl butanoate), diospyrin-2'-(2hydroxypropanoate), and diospyrin-3'-(2 hydroxypropanoate), from the acetone extract of heartwood and bark of *D. montana*, in conjunction with this diospyrin-2'-(2-epoxy-3-methyl butanoate) was reported for the first time. Puri (2020) isolated a significant amount of pentacyclic triterpenes from the ethanolic fraction of *D. montana* leaves. These isolated compounds were identified as oleanolic acid and as β -amyrin derivatives of pentacyclic triterpenes, by comparison with spectral data from the literature.

23.3 BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

Reports on *in vivo* and *in vitro* bio-assay of different *Diospyros montana* extracts began in 1952 and appeared mostly during 1970–1980. Almost all parts of *D. montana* plant are utilized in the treatment of various diseases is shown in Table 23.2. Broad screening of *D. montana* has ascribed to a wide array of pharmacological activities.

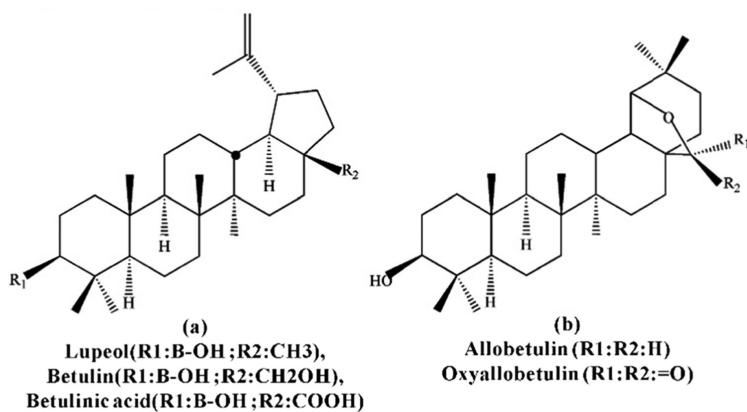


FIGURE 23.1 Lupane type triterpenes.

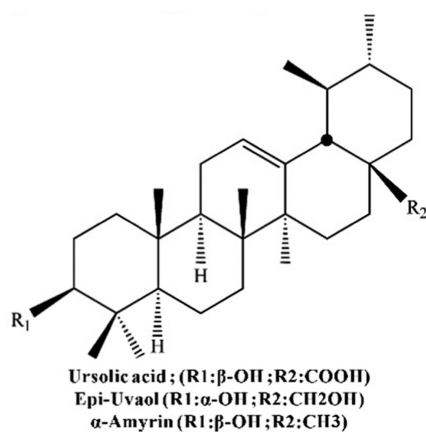


FIGURE 23.2 Ursane type triterpenoid metabolites.

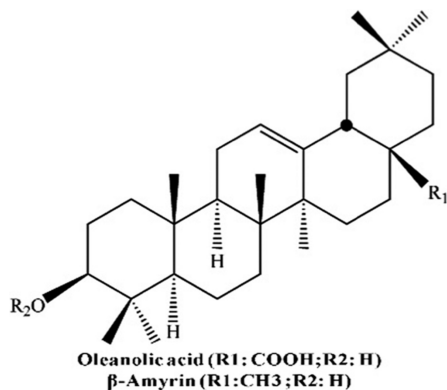


FIGURE 23.3 Oleanane type triterpenes.

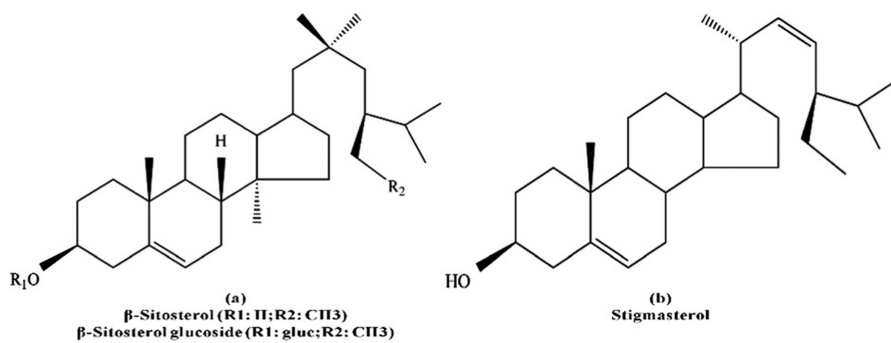


FIGURE 23.4 Steroidal skeletons.

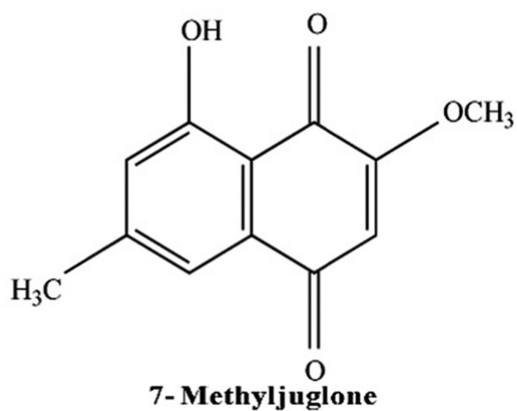


FIGURE 23.5 Methyljuglone.

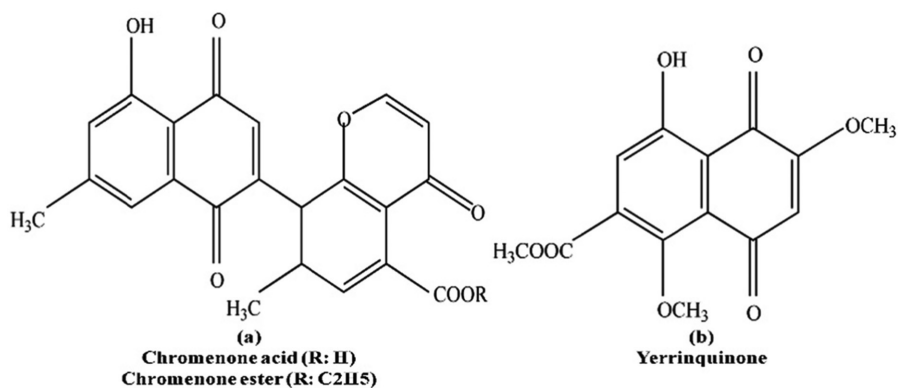


FIGURE 23.6 Monomeric 1,4-naphthoquinone.

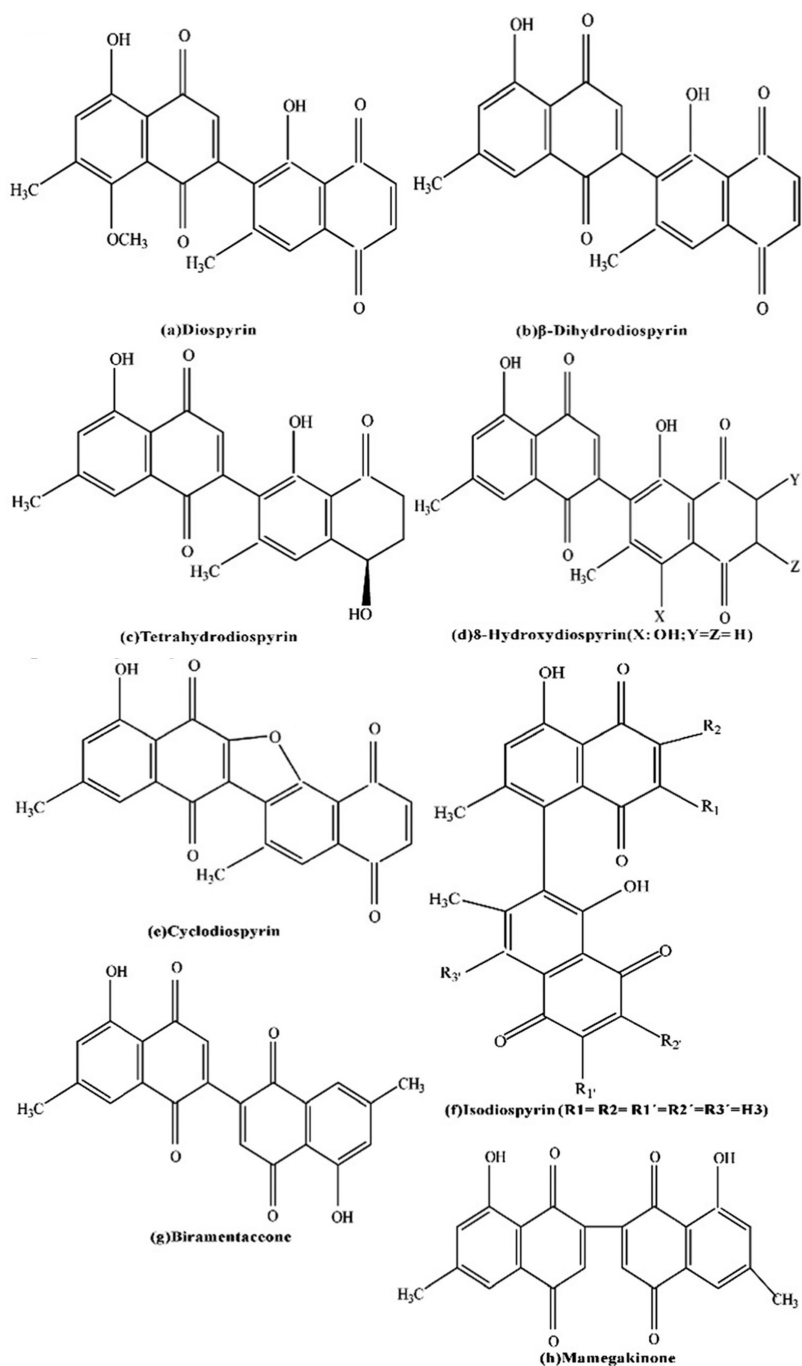


FIGURE 23.7 Naphthoquinone derivatives.

TABLE 23.1 Phytochemicals of *D. montana*

SL. No.	Part of Plant	Isolated Phytoconstituents	References
1.	Bark	Naphthoquinones	Sarma et al. (2007); Tezuka et al. (1973)
2.		7-methyljuglone tetrahydrodiospyrin	Pardhasaradhi et al. (1979)
3.		8-hydroxydiospyrin	Lillie et al. (1976)
4.		Flavonol glycosides	Tanaka et al. (2007)
5.	Leaves	Diospyrin	Hazra et al. (2002)
6.		Cyclodiospyrin	Lillie et al. (1976)
7.		β -sitosterol	Kumar (2009)
8.		Oleanolic acids and β -amyrin	Puri (2020)
9.	Fungal-infested stems	Yerrinquinone	Pardhasaradhi et al. (1990)
10.	Seeds	Hydroxyoctadec-10 (z)-enoic acid	Rauf et al. (1987)
11.	Fruit pulp	Oleanolic and betulinic acids, α -amyrin	Mallavadhani et al. (1998)
12.	Root	Triterpenoids	Misra et al. (1972)
13.		Diospyrin	Likhitwitayawuid et al. (1999)

TABLE 23.2 Biological Activities of *D. montana*

SL. No.	Part of Plant	Activity Reported	References
1.	Seeds	Antibacterial	Goutam and Purohit (1973)
2.	Heartwood	Antioxidant	Pathak et al. (2009)
3.	Bark	Antipyretic	Rastogi and Mehrorta (1990–1992)
4.		Antimicrobial	Dey et al. (2014)
5.		Antimalarial	Hazra et al. (1995)
6.	Fruits	Anticancer	Sarma et al. (2008)
7.		Antifilarial activity	Kumar et al. (2009)
8.	Stem-bark	Topoisomerase-I Inhibition	Tazi et al. (2005); Norhanom et al. (1997); Pal et al. (1996)
9.		Anti-tubercular	Dey et al. (2014)
10.		Anti-Leishmaniasis	Yardley et al. (1996)
11.	Roots	Anthelmintic	Rajarajeshwari et al. (2010)
12.		Antimalarial	Likhitwitayawuid et al. (1999)
13.	Leaves	Free radical scavenging	Puri et al. (2010); Puri (2019)

23.3.1 Antimicrobial Activity

Singh et al. (2005) evaluated the effect of *D. montana* leaf extracts on *Escherichia coli*, *Bacillus subtilis*, *Corynebacterium pyrogens*, *Pasteurella multocida*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Salmonella pullorum*, *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus niger*. All the bacteria were effectively inhibited on treatment with different extracts of *D. montana* leaf. Goutam and Purohit (1973) determined antibacterial activity against 48 strains of microorganisms, where petroleum ether and chloroform extracts showed potent activity against *Bacillus subtilis* and *Corynebacterium pyrogens*. Dhawan et al. (1980) assessed the antibacterial activity against *Bacillus subtilis* and *Corynebacterium pyrogens*. Kokila et al. (2017) reported a plant-intervened synthesis of selenium nanoparticles (Se-NPs) utilizing the aqueous extract of *D. montana* by a simple precipitation technique. Nanoparticles suspensions displayed critical antimicrobial activity against two microorganisms, for example, gram-positive *Staphylococcus aureus*, gram-negative *Escherichia coli* (bacteria), and fungi *Aspergillus niger*. Bharathi et al. (2018) reported the antibacterial activities of eco-friendly biosynthesized silver nanoparticles (AgNPs) from the stem bark extract of *D. montana*. The *in-vitro* antibacterial activity of different concentrations of AgNPs was examined against both gram-positive (*B. subtilis* and *S. aureus*) and gram-negative (*E. coli* and *P. aerogenes*) bacterial strains. The results displayed significant antibacterial activity of the biosynthesized AgNPs. Siddiqi et al. (2019) synthesized AgNPs from aqueous extract of *D. montana* and determined their antibacterial activity against nine different bacterial strains using the agar well and disk diffusion method. This study showed maximum activity of Ag-NPs was against *Klebsiella pneumoniae* and *Escherichia coli*. They also have observed a resistant pattern against *Streptococcus viridans* and *S. mutans*.

23.3.2 Antimycobacterial Activity

Mukanganyama et al. (2012) evaluated the antimycobacterial action of diospyrin and four of its derivatives (D1, D2, D5, D7, and D17) against the nonpathogenic *Mycobacterium aurum*. The impact of these compounds was determined on growth parameters and drug efflux pumping activity. The antimycobacterial activity was determined using the agar disk diffusion method with standard drug rifampicin. Diospyrin appeared to be the most

potent in repressing the growth of *M. aurum* and was more active than all its derivatives. The compounds were bacteriostatic rather than bactericidal, as the minimum bactericidal concentration (MBCs) was more prominent than 50 µg/mL. Lall et al. (2003) reported that three derivatives and one structural analog of diospyrin, which were synthesized and investigated for their inhibitory activity against *M. tuberculosis* utilizing the fast *in-vitro* radiometric method. A novel amino acetate derivative was observed to be more dynamic than the parent compound, respectively for a drug-susceptible strain, H37Rv, of *M. tuberculosis*. This derivative additionally exhibited a minimum inhibitory concentration (MIC) for a couple of multidrug-resistant strains of *M. tuberculosis*. Dey et al. (2014) investigated the therapeutic effect of diospyrin, as an antimicrobial agent against a broad panel of multi-drug and extensively drug-resistant tuberculosis strains (M/XDR-TB) strains, rapid growing mycobacteria, and other bacterial isolates, some of which were producers of β -lactamase, extended-spectrum β -lactamase (ESBL), AmpC β -lactamase, metallo-beta-lactamase (MBL) enzymes, as well as their drug-sensitive ATCC counterparts. All the tested quinones showed antimycobacterial and broad-spectrum antibacterial activity, principally against *M. tuberculosis* and gram-positive bacteria of clinical origin.

23.3.3 Antioxidant Activity

Pathak et al. (2009) determined the free radical scavenging activity of the methanolic extract of *D. montana* heartwood by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and reducing power method. Ascorbic acid, which was used as a standard, showed an inhibitory concentration (IC₅₀) of 174.7 µg/mL, whereas the heartwood extract of *D. montana* exhibited an IC₅₀ of 115.31 µg/mL. Puri et al. (2010) screened various extracts of *D. montana* leaves for *in-vitro* free radical scavenging activity utilizing DPPH and superoxide radical scavenging activity. The results showed that each of the extracts and their fractions possessed concentration-dependent free radical scavenging activity. Puri (2019) determined the free radical scavenging potential of the ethanolic extract and its fractions of *D. montana* using parameters such as superoxide radical scavenging, nitric oxide inhibition, and β -carotene/linoleic acid antioxidant activity. Ethanolic extracts and its ethyl acetate (EtOAc) fraction showed significant antioxidant activity compared to petroleum ether, chloroform fraction, and well-characterized standard antioxidant systems *in vitro*.

23.3.4 Anticancer Activity

Hazra et al. (1981) reported that the simple ethanolic extract of the *D. montana* bark showed significant regression in the growth of *Ehrlich ascites carcinoma* (EAC) in Swiss Albino mice and the hematological parameters of tumor-bearing mice was significantly restored to the ordinary range. Hazra et al. (1984), based on their previous findings, studied the effect of bis-naphthoquinone derivative, diospyrin as a biologically active principal compound that was extracted from the bark of *D. montana*. This compound diospyrin inhibited the *in-vivo* growth of EAC, in Swiss A mice. Sarma et al. (2008), for the first time, described the tumor-inhibitory activity of diospyrin and its series of derivatives, amino-naphthoquinones, which were isolated from *D. montana*. Among this amino acetate, the derivative demonstrated the most extreme increase in lifespan *in-vivo* against murine EAC at a dose of 1 mg/kg/day (IP; five doses), and the lowest (IC₅₀) (0.06 mM) *in-vitro*. Later, the same analog also exhibited a considerable enhancement in antiproliferative activity when evaluated against human cell lines, viz. malignant skin melanoma and epidermoid laryngeal carcinoma, in contrast to the characteristic precursor, diospyrin. Here, diospyrin, and its derivatives showed severe cytotoxicity against tumor cells as compared to normal human lymphocytes. These quinonoids produced considerable amounts of reactive oxygen species in EAC cells, more or less equal to their corresponding IC₅₀ values. Sarma et al. (2007) reported that the derivatization of diospyrin isolated from *D. montana* led to the modification of its inhibitory *in-vitro* activity. Among the novel derivatives, epoxide showed the supreme antiproliferative activity and a similarly decreased toxicity in normal human peripheral blood mononuclear cells (PBMC). Tazi et al. (2005) validated topoisomerase-I as an objective for diospyrin and, for the first time exemplified structure-activity relationships for topoisomerase-I inhibition by this group of bisnaphthoquinoids. Norhanom et al. (1997) isolated diospyrin and derivatives from the stem bark of *D. montana*, followed by purification and characterization. Diospyrin and its two derivatives were subjected to *in-vitro* assay for inhibition of tumor promotion utilizing initiation of *Epstein-Barr* virus (EBV) early antigen (EA) expression in the EBV genome conveying human lymphoblastoid cells. Here, synthetically modified diospyrin indicated positive outcomes against tumor promotion by restraining EBV-EA expression in Raji cells induced by 12-O-Tetradecanoylphorbol-13-acetate (TPA). Pal et al. (1996) isolated diospyrin (I) from the stem bark and its derivatives, namely II, III, IV, and V, and confirmed noteworthy *in-vivo* inhibitory activities against murine tumors. These studies were completed after treatment with diospyrin and four synthetic

derivatives. Hematological status, several serum glycolytic enzymes, serum protein, creatinine levels, and histopathology of the mice that were inoculated with EAC. The analytical significance of the pharmacological studies has been reflected through these experiments, which reveal the tumor-inhibitory properties of diospyrin and its derivatives.

23.3.5 Anti-Filarial Activity

Kumar et al. (2009a) investigated the screening of fruits of *D. montana* for anti-filarial activity. An *in-vitro* study was carried out to see the effects of extracts on both the entire worm (w/w) and on nerve-muscle preparation of *Setaria cervi*, on the survival of microfilariae. Initial stimulation was produced by petroleum ether extract followed by reversible paralysis in the whole worm. This stimulation was not seen with petroleum ether during nerve-muscle preparation. The alcoholic extract showed reversible paralysis in the entire worm through the irreversible response in nerve-muscle preparation. Kumar et al. (2009) studied the effect of petroleum and alcoholic extract of stem wood of *Diospyros montana* on the spontaneous movements of the whole worm preparation and nerve-muscle complex of *cattle filarial* parasite *Setaria cervi* and the effect on survival of *microfilariae*. Petroleum extract of stem wood showed spontaneous inhibition in both the whole worm and the nerve-muscle preparation, whereas alcoholic extract of stem wood had only shown an effect on the nerve-muscle preparation. The lethal concentration 50 (LC50) and 90 (LC90) for petrol extract were 25 ng/ml and 35 ng/ml, respectively.

23.3.6 Antiplasmodial Activity

Likhitwitayawuid et al. (1999) extracted the roots of *D. montana* with EtOAc and subjected to the chromatographic separation that led to the isolation of diospyrin and 5-hydroxy-4-methoxy-2-naphthaldehyde. Isolated diospyrin showed significant *in-vitro* antimalarial activity by inhibiting the growth of *Plasmodium falciparum* at 2,500 IC₅₀ (ng/mL). Hazra et al. (1995) isolated diospyrin stem bark of *Diospyros montana* and subjected to methylation, reduction, and acetylation that yielded semisynthetic derivatives named as diospyrin (I), dimethyl ether (II), tetra-hydroxy (III) and tetraacetoxy (IV). A multidrug-resistant K1 strain of *Plasmodium falciparum* was used in the determination of antiplasmodial activity. The investigations exhibited that

out of four other compounds tested, two, (I) and the (II), presented a relatively low degree of activity, the dimethyl ether showed good activity. Compound (III) and (IV) analogs that were synthesized by stepwise chemical modification, had a similar degree of antiplasmodial activity, here compound (III) being slightly more active than IV), and were two orders of magnitude, about 100-fold, more active than diospyrin.

23.3.7 *Anti-Leishmanial Activity*

Yardley et al. (1996) evaluated diospyrin and its synthetic derivatives *in-vitro* against intracellular amastigotes of *Leishmania donovani* and *Trypanosoma cruzi* in macrophages and extracellular *Trypanosoma brucei* bloodstream form trypomastigotes. Diospyrin did not show any activity against *L. donovani*. The dimethyl ether derivative was more dynamic than the parent compound, yet the hydroquinonoid form was the most dynamic anti-parasitic agent against *L. donovani*. Hazra et al. (2002) isolated Diospyrin (I) from the stem bark of *D. montana* and its derivatives naphthoquinonoid, which was converted into an analogous dimeric compound. The inhibitory activity of all these products was estimated against *Leishmania major* promastigotes. The growth inhibition of the parasites was estimated by measuring the resultant radioactivity on the filters in the control and the test compound-treated wells. Modifications in the structure of diospyrin (I) produced variable effects. Compounds II and V were the most effective, causing nearly 98% inhibition at a dose of 2.5 mg/mL. While all the derivatives (II-VI) showed enhanced antileishmanial activity in comparison to their precursor (I), the dimeric analog, (VII) was found to be inactive in the assay. Ray et al. (1998) showed a noteworthy inhibitory effect of diospyrin on the growth development of *L. donovani* promastigotes. This compound restrains the catalytic activity of DNA topoisomerase I in the parasite. Treatment of DNA with diospyrin before the expansion of topoisomerase-I is not affected, with diospyrin before the expansion of DNA to the unwinding response expands this restraint. Preincubation of topoisomerase-I with diospyrin before the expansion of DNA to the unwinding response expands this inhibition. An examination demonstrated that this bis-naphthoquinone compound exerts leishmaniasis presents as a spectrum of diseases, extending from benign cutaneous lesions through metastasizing mucocutaneous structures to the regularly deadly visceralizing structure. Diospyrin demonstrated a particular inhibitory effect on the parasitic topoisomerase-I of *L. donovani*. These outcomes demonstrated a powerful inhibitory effect of diospyrin on type-I

DNA topoisomerase from *L. donovani*, which can be subjugated for rational drug design in human leishmaniasis.

23.3.8 Anthelmintic Activity

Rajarajeshwari et al. (2010) assessed *in-vitro* anthelmintic activity of leaf and root extracts of *D. montana* on adult earthworms, where different concentrations showed a significant effect on the paralysis of worms.

KEYWORDS

- high-performance thin-layer chromatography
- metallo-beta-lactamase
- minimum bactericidal concentration
- minimum inhibitory concentration
- peripheral blood mononuclear cells
- *Diospyros montana*

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CHAPTER 24

Bioactives and Pharmacology *Carissa spinarum* L.

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24.1 INTRODUCTION

Carissa spinarum L. (Synonyms: *Carissa diffusa* Roxb., *C. ovata* R.Br., *C. brownii* F. Muell., *C. edulis* (Forssk.) Vahl, and *C. opaca* Stapf ex Haines) belongs to Apocynaceae family also known as dogbane family. *C. spinarum* is a thorny evergreen shrub commonly known as Bush Plum, Wild Karaunda and Garanda but different common names are used in different areas such as blackcurrant in Australia and *Enkeldoring-noemnoem* in Africa. It is a native plant of Australia but frequently found in dry subtropical regions of Southern central Asia and Africa. It is abundantly found in subtropical scrub-type vegetation especially in Pakistan due to its drought-resistant nature usually along low hills with *Acacia modesta* and *Olea ferruginea*. It is highly fodder for goat and sheep, medicinal, and fuelwood plant. It is a profusely branched, woody, large shrub with long, single, or branched thorns, having grayish rough or smooth bark. Branches and leaves with white milky latex; Leaves usually notched, ovate with acute or round apex; petiole 0.5–6 mm long. Inflorescence terminal or sometimes axillary with many-flowered cymes. Flowers white sweet-scented, bisexual; calyx polysepalous, with 5 sepals, green; corolla tubular at the base of flowers, pentamerous; ovary superior with spindle stigma. Fruits reddish to black, globose, or oval shape. Fruits ripen during autumn and locally used in curing ailments like tonic, inflammation, liver disorders, myocardial infarction, fevers, etc. Leaves and fruits are used to cure liver diseases, asthma, and lungs problems and infection.

Roots are also useful in treating cattle, goat, and sheep diseases (Marcola, 2014; Ajaib, 2012).

24.2 BIOACTIVES

The basic phytochemical analysis of leaves methanolic extract of *C. spinarum* revealed flavonoids, alkaloids, anthraquinones, terpenoids, coumarins, tannins, phlobatannins, and cardiac glycosides. The HPLC analysis of leaves methanolic extracts confirms the presence of myricetin, isoquercetin, vitexin, hyperoside, and kaempferol type flavonoids (Sehreen et al., 2011).

C. spinarum seeds contained volatile oil, protein, and fatty acids (Fatima et al., 2013; Rai et al., 2006; Kumar et al., 2009). The chloroform extract of stem contains lignans (Rao et al., 2005). Stem methanol extract contains cardiac glycosides digitoxigenin-3-O- β -d-digitalopyranoside (Wangteeraprasert et al., 2014). Root extract contains stigmasterol, campesterol limonene, β -sitosterol, lupeol, and flavonoids (rutin and quercetin) (Hedge et al., 2012; Ahmed et al., 2015; Raina et al., 1973).

The separation of ursolic acid (i) isolated from the leaves, Rutin (ii) and kaempferol (iii) isolated from the leaves, bark, and fruits of *C. spinarum*, possesses hypertension, anti-inflammatory, and anti-diuretic activities (Mathuram and Brahmahayalaselvam, 1998). The naphthalenone (iv) was isolated from the roots of *C. spinarum* (Youssef and Hassan, 2010) whereas a cyclohexanhexol, pinitol from the leaves extract (Hanan and Wafaa, 2012). In addition, four esters, 3-(4-methoxyphenyl)-3-oxo-propionyl hexadecanoate (v) and 2-benzene dicarboxylic acid mono (2-ethylhexyl) (vi) ester were obtained from *C. spinarum* (Saeed and Ahmed, 2015). Only two cardiac glycosides were earlier identified from the roots of *C. spinarum* (Figure 24.1) (Wangteeraprasert et al., 2012). From the stems of *C. spinarum*, 12 potent compounds were recognized presented in Figure 24.2 (Wangteeraprasert et al., 2012).

24.3 PHARMACOLOGY

C. spinarum is much explored and known to possess an excellent pharmacological importance due to its ethnic interaction in history. It possesses an extensive type of phytochemicals in both vegetative and floral parts. The pharmacological importance using various methods both *in vivo* and *in vitro* had been carried by many workers throughout world, and some of the important activities are listed below.

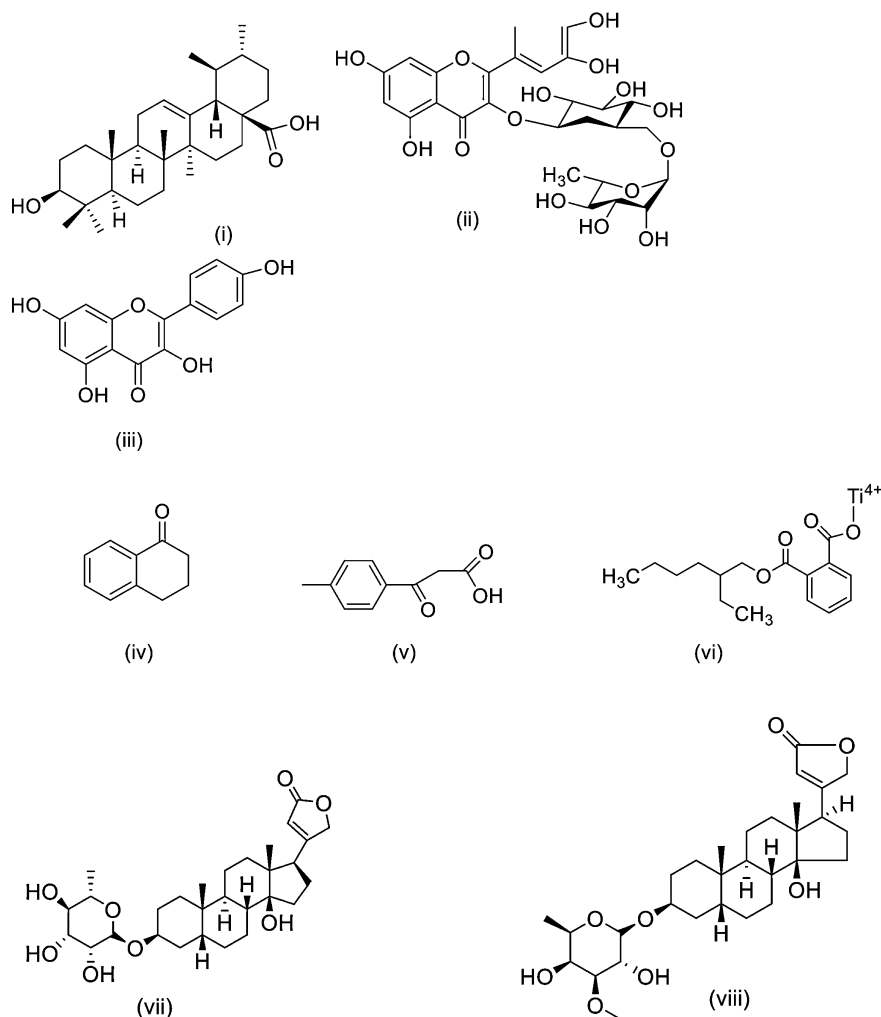


FIGURE 24.1 Ursolic acid (i); rutin (ii); kaempferol (iii); naphthalenone (iv); 3-(4-methoxyphenyl)-3-oxo-propionyl hexadecanoate (v); 2-benzenedicarboxylic acid mono (2-ethyl-hexyl) (vi); evomonoside (vii); and odoroside H (viii).

24.3.1 Anthelmintic Activity

According to Harwansh et al. (2010), adult Indian earthworm *Pheretima posthuma* death and paralysis possesses almost the same time with standard drug piperazine at 100 mg/mL of crude methanolic extract.

24.3.2 Antiarthritic Activity

Ethanollic extract of *C. spinarum* root at 400 mg/kg doses effectively displayed antiarthritic potential in Freund's adjuvant-induced polyarthritis in rats as compared to phenylbutazone standard. It was noticed in this study that plant extract had significant, dose-dependent antiarthritic activity (Hegde et al., 2010).

24.3.3 Anticonvulsant Activity

Ya'u et al. (2008) demonstrated significant anticonvulsant potential of hydroalcoholic extract of root of *C. spinarum* in pentylenetetrazole (PTZ)-induced convulsion in mice. For anticonvulsant screening, 20 mg/kg of hydroalcoholic extract was given through IP route and effectively reduced convulsions comparative to naloxone and diazepam were standard drugs.

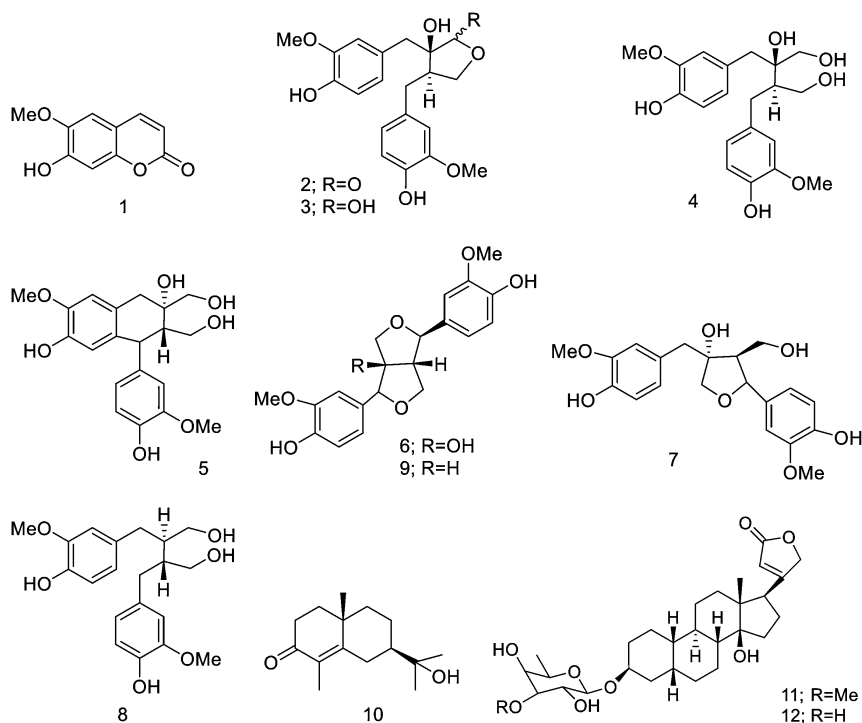


FIGURE 24.2 Structures of compounds scopoletin (1); (–)-nortrachegenin (2); (–)-carissanol (3); (–)-carinol (4); (+)-cycloolivil (5); (+)-8-hydroxypinoresinol (6); (–)-olivil (7); (–)-secoisolariciresinol (8); (+)-pinoresinol (9); carissone (10); digitoxigenin-3-*O*-β-D-digitalopyranoside (11); and evomonoside (12); isolated from *C. spinarum*.

24.3.4 Antidiabetic Activity

The potential ethanolic extract of leaves of *C. spinarum* in streptozotocin (STZ) diabetic adult male albino rats. The extract showed significant antidiabetic activity in comparison with the reference drugs metformin and glibenclamide (EI-Fiky et al., 1995).

24.3.5 Anti-Inflammatory Activity

Aqueous extracts of leaves of *C. spinarum* at oral dose of 200 mg/kg to formalin induced albino rats reduce significant inflammation juxtaposed to standard drug Analgin (30 mg/kg) (Beck and Namdeo, 2016).

24.3.6 Antioxidant Activity

Sahreen et al. (2010) showed considerable antioxidant activities but lesser than ascorbic acid might be due to crude form of plant. Synthetic derivatives of carenone isolated by Rao et al. (2006) showed potent anti-oxidative property. The extract of root powder with 70% ethanol and antioxidant potential was conducted on the basis of total phenolic content, reducing power, 2, 2-diphenyl-1-picryl-hydrazyl-hydrate assay, and lipid peroxidation. The extract showed significant antioxidant activity though it is not as potent as standard drugs (Woode et al., 2007). Hegde and Joshi (2010) evaluated ethanolic extracts of *C. spinarum* roots for in chloroform-induced as well as paracetamol (PCM)-induced hepatotoxicity. The livers were processed after sacrificing animals and tested for antioxidant activity for reduced glutathione (GSH) estimation, superoxide dismutase (SOD), and lipid peroxidation of malondialdehyde (MDA). The results were found to as decreased levels of GSH and MDA, as well as a significant rise in hepatic SOD.

Khan et al. (2010) studied the antioxidant activity of leaves of *C. spinarum* with different extracts, i.e., petroleum ether (COE-PE), chloroform (COE-CH), ethyl acetate (COE-EA), acetone (COE-AC), methanol (COE-ME), n-butanol (COE-BU) and water (COE-WA). The antioxidant potential of *C. spinarum* extracts (COEs) was evaluated by ferric thiocyanate, thiobarbituric acid, scavenging of DPPH, and total phenolic methods. The results revealed that COEs had a good antioxidant effect (inhibition of lipid peroxidation > 50%) and DPPH \cdot scavenging potential (scavenging > 80%). These results

indicate that leaves extract of *C. spinarum* possess significant antioxidant potential.

24.3.7 Antimicrobial Activity

The distilled water extracts of leaves and fruits were more aggressive against gram-negative as compared to gram-positive might be due to structural difference between them (Ibrahim et al., 2005, 2010). Antimicrobial activity was reported by Shahada et al. (2014) by preparing plant extracts in various solvents by cold maceration method. Various extracts of fruit of *C. spinarum* at different concentrations and noticed ethanolic extract to be having highest efficacy, followed by acetone and ethyl acetate (EtOAc). The degree of inhibition was found highest in *Streptococcus pyogenes* (Chandra et al., 2011; Ngulde et al., 2013).

24.3.8 Antileishmanial Activity

Njau et al. (2016) evaluated preliminary antileishmanial activity of *C. spinarum* extracts carried on promastigote form of *Leishmania major* and methanolic extracts at high concentrations (200 µg/ml) appeared good IR values not effectively different to the standard reference drug pentostam at concentration 50 µg/ml.

24.3.9 Antiplasmodial Activity

Kebenei et al. (2011) investigated the antiplasmodial potential of nortrachelogenin, a compound which is separated from the root of *C. spinarum* and found that the compound has potential to be the cheap antimalarial drug, and also proves the ethnopharmacological use. Ayuko et al. (2009) screened the root bark extract and stem bark extract on CQ-sensitive and CQ-resistant strains of *Plasmodium falciparum*. The result of this study showed that the plant has mild antimalarial activity.

24.3.10 Antiviral Activity

Tolo et al. (2006) demonstrated the antiviral potential of aqueous extract of root bark of *C. spinarum* against HSV (herpes simplex virus), at different parameters such as plaque inhibition assay and virus yield reduction assay against Balb/C mice cutaneous infected with HSV. In plaque inhibition

assay, the result showed that instead of wild type strains, the resistant strains were more susceptible to the extract. In yield reduction, assay 200 g/ml dose of the extract effectively reduced 100% virus yield of APr HSV-1.

24.3.11 Cytotoxicity Studies

In vitro cytotoxicity studies on *C. spinarum* extracts by sulforhodamine-B assay method were evaluated by Doshi and Une (2015) and Sehar et al. (2011). *C. spinarum* extract showed equivalent activity comparable to the standard compound ADR for human breast cancer cell line MCF7, and also showed mild progressive activity on other two selected cell lines, i.e., human colon cancer cell line HCT15.

24.3.12 Diuretic Activity

Nedi et al. (2004) and Kebamo et al. (2015) evaluated the diuretic effect of the root bark of the plant in albino Wistar rats with 80% methanol. The extract used in this study was root bark maceration extract and root bark Soxhlet extract. The root bark maceration extract failed to show any significant diuretic activity, but root bark Soxhlet extract showed the significant diuretic activity.

24.3.13 Erythropoietic Effect

Ethanollic root extract of *C. spinarum* against phenylhydrazine-induced anemia in Sprague Dawley rats at dose 1000 mg/kg, while 0.23 ml/kg bioferon acts as a reference drug. *C. spinarum* at dose 1000 mg/kg was able to reverse very significantly anemia caused by phenylhydrazine after 45 days of treatment without anisocytosis (Koffuor et al., 2012).

24.3.14 Hepatoprotective Activity

Ethanollic extracts of *C. spinarum* roots effectively reduced PCM-induced hepatotoxicity as compared to control groups at 400 mg/kg (Hegde and Joshi, 2010). Similar studies were conducted by Sahreen et al. (2011), but instead of roots, leaves were selected for screening of potential hepatoprotective

activity. CCl_4 decreases the effects of hepatic antioxidant enzymes increases the activity of serum marker enzymes and also significantly increases the hepatic thiobarbituric acid reactive substances (TBARS) and H_2O_2 but animals pre-treated with 200 mg/kg of methanolic extract of *Carissa* leaves increased activity of hepatic antioxidant enzymes and also prevents alteration in TBARS, H_2O_2 , GSH, and protein content.

24.3.15 Wound Healing

A balm of the methanolic extract of *C. spinarum* root, revealed a pro-healing effect when externally applied on mice the healing process become speed up juxtaposed with the control group, suggesting that the plant has significant wound healing activity (Sanwal and Chaudhary, 2011).

24.3.16 Antihyperlipidemic Effects

Fatima et al. (2013) analyzed that acetone extract of leaves effectively lowers the triglycerides and HDL cholesterol in diabetic rats.

KEYWORDS

- *Carissa spinarum*
- herpes simplex virus
- malondialdehyde
- paracetamol
- pentylenetetrazole
- *Carissa opaca*
- *Carissa edulis*

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CHAPTER 25

Chemical Characterization and Pharmacology of *Salsola imbricata* Forssk.

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25.1 INTRODUCTION

Salsola imbricata Forssk. belongs to family Chenopodiaceae. It is widely distributed in Central and North Africa, Pakistan, Iran, India, Afghanistan, and Egypt. It is a small shrub about 0.3–1.2 m in height. *Salsola imbricata* commercially used for the manufacturing of alkali and eaten by camels (Munir et al., 2014). The common synonyms of this species are *Salsola foetida* Del., *Salsola baryosma* Schult., *Chenopodium baryosmum* Schult. and *Caroxylon foetidum* Moquin whereas its common names are Harm, Alghtraf, Khareet, Chaundhary, el-Chret, Arkam, Lana, Lani, and Khaar. It is used to cure of dysentery, cold, indigestion, diarrhea, and asthma and as a female contraceptive (Malik et al., 2015; Ahmed et al., 2014), Vermifuge, diuretic as well as anti-inflammatory (Farooq et al., 2008; Al-Saleh et al., 1993). The people of the UAE use *S. imbricata* for contraception purposes and as smother for cleaning sinuses, anthelmintic, and lightening itched skin in Saudi Arabia (Hammich and Maiza, 2006; Al-Ghonaimi, 1993).

25.2 BIOACTIVES

Ajaib et al. (2019) indicated the occurrence of alkaloids, saponins, flavonoids, tannins, reducing sugar anthraquinone and cardiac glycosides by

qualitative phytochemical analysis. Anthraquinone present in some extracts, whereas flavonoids present in all extracts except aqueous fruit extract. The phytochemical qualitative screening revealed terpenoids, saponins, anthraquinones, and tannins, reducing sugars, cardiac glycosides, flavonoids, phenol, and alkaloids.

Shehab and Abu-Gharbieh (2014) reported qualitatively and quantitatively phenolic composition (flavonoids and phenolic acids) in methanolic extract of *S. imbricata*. Spectrophotometry is used to determine the efficacy of various solvents containing total phenolic and flavonoid contents in this plant. At 280 nm the total 13 components were recognized that is equivalent to 13.904% of total composition out of 13, nine were phenolic acids (9.734%) with occurrence of coumaric acids (4.251%) and (catechin and chrysin) two are flavonoids and diphenol, catechol, and one nonphenolic benzoic acid (2.306%). On the other hand, at 330 nm, total 8 components recognized included 7 are flavonoidal nature the most important (12.692%) quercetin and 2.734% amount of rosmarinic acid. According to Turki, (1999) the protein, lipid, and neutral sugars in *S. imbricata* restrained 392.7 mg/gm, 28.0 mg/gm, and 68.0 mg/gm and only 0.1% capric acid measured.

Osman et al. (2016) isolated nine phenolic compounds from the leaves of *S. imbricata* amongst them two new compounds isorhamnetin-3-O- β -D-glucuronyl (1'' \rightarrow 4'') glucuronide (1) and its dimethyl ester; isorhamnetin-3-O- β -D-di glucuronate dimethyl ester (2).

(1) isorhamnetin-3-O- β -D-glucuronyl (1'' \rightarrow 4'') glucuronide and (2) Isorhamnetin-3-O- β -D-glucuronate methyl ester (1'' \rightarrow 4'')- β -glucuronate methyl ester were isolated from the leaves of *S. imbricata* using chromatographic analysis. Two new secondary metabolites namely, salisomide, and salisoflavan were identified from the alcoholic extract of aerial part of *S. imbricata* and their structures recognized by using spectroscopic procedures including heteronuclear single quantum correlation (HMQC), correlated spectroscopy (COSY) and heteronuclear multiple bond correlation (HMBC), Nuclear magnetic resonance (NMR) tests (Figure 25.1). (i) Salisomid (ii) Salisoflavan (Figure 25.2) were isolated from the aerial part of *S. imbricata* (Saleem et al., 2009).

Oueslati et al. (2017) reported two bioactive (i) biphenylpropanoids and (ii) biphenylsalsonoid, respectively from the roots of *S. imbricata* through phytochemical investigation (Figure 25.3). Hamed et al. (2011) analyzed the phytochemical analysis of root of *S. imbricata* isolated the two triterpene glycosides derivatives along with three known compounds and their structures represented through spectroscopic methods (Figure 25.4).

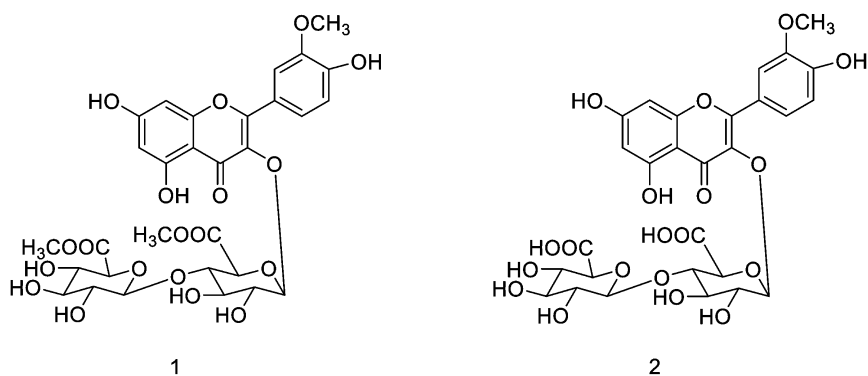


FIGURE 25.1 Isorhamnetin-3-O-β-D-glucuronide (1^{'''}→4^{''}) glucuronide (1); and its dimethyl ester (2) (Reprinted from Osman et al., 2016).

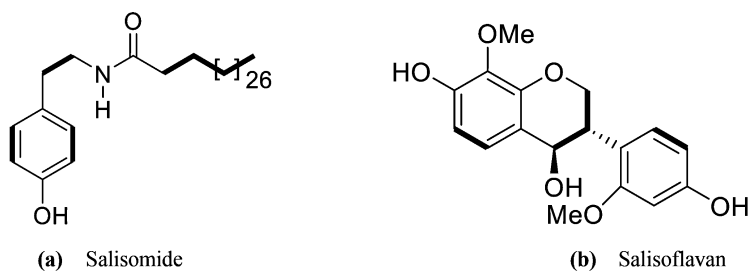


FIGURE 25.2 (a) Salisomide; (b) salisoflavan (Saleem et al., 2009).

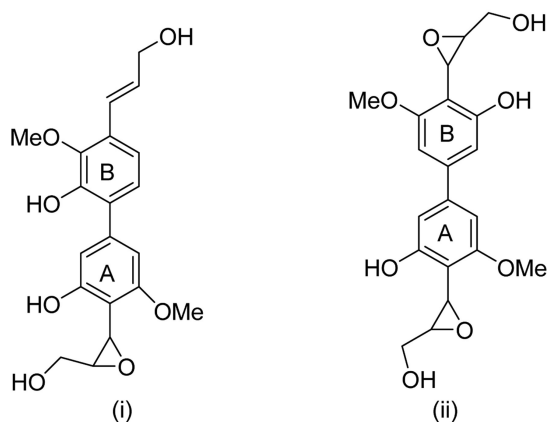


FIGURE 25.3 (i) biphenylpropanoids; and (ii) biphenylsalsonoid. (Adapted from Oueslati et al., 2017)

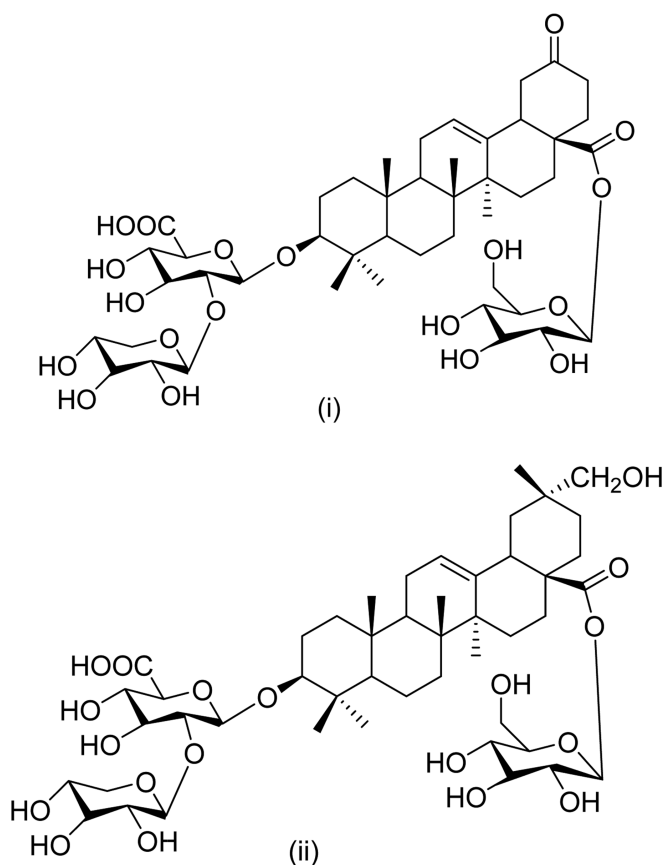


FIGURE 25.4 3-O-b-D-xylopyranosyl-(1!2)-O-b-D-glucuronopyranosylakebonic acid 28-O-b-D-glucopyranoside (i); and (ii) 3-O-b-D-xylopyranosyl-(1!2)-O-b-D-glucuronopyranosyl-29-hydroxyoleanolic acid-28-O-b-D-glucopyranoside. (Reprinted with permission from Hamed et al., 2011. © Elsevier.)

Ahmed et al. (2008) reported the phytochemical analysis revealed that the triterpenes Salsolins A (i) and B (ii) isolated from *Salsola baryosma* syn. of *Salsola imbricata* chloroform resolvable portion along with 2 α ,3 β ,23,24-tetrahydroxyurs-12-en-28-oic acid (3) reported for the first time from this species by spectroscopy methods (Figure 25.5). Munir et al. (2014) detailed work Pharmacognosy of genus *Salsola* and performed phytochemistry of leaves extracted with methanol and chloroform using microscopy, macroscopy, and physicochemical parameters.

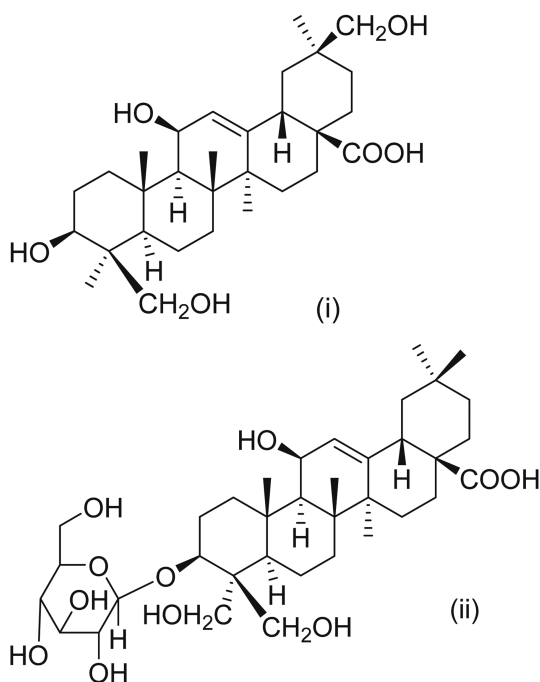


FIGURE 25.5 Structures of Salsolins A (i); and B (ii).

25.3 PHARMACOLOGY

25.3.1 Anthelmintic Activity

Ajaib et al. (2019) evaluated the anthelmintic activity of chloroform extract of bark and fruit of *S. imbricata* and in this purpose the parasitic test organisms, i.e., *Haemonchus contortus* obtained from dissection of freshly slaughtered goat abomasum and then using 0.9% NaCl solution washed the abomasum. Anthelmintic activity was evaluated by detecting the paralysis and death time of worm at different fractions. At conc. of 100 mg/ml bark chloroform extract acquired the least time for paralysis and death of worms (9 ± 0.6 and 13 ± 0.2 min) while at concentration of 20 mg/ml greatest time occupied by chloroform extract of bark for paralysis 96 ± 1.5 and for death, i.e., 137 ± 0.7 by petroleum ether extract of bark. At concentrations of 100 mg/ml, the chloroform extract of fruit exhibited the lowest time for paralysis and death of worms, i.e., 10 ± 1.1 min and 16 ± 0.1 min, while at 20 mg/

ml largest time consumed by chloroform extract of fruit for paralysis, i.e., (97 ± 0.8 min.) and for death (135 ± 0.4 min.) by petroleum ether extract of fruit and aqueous extract exhibited lowest time for death, i.e., 100 ± 1.5 min. Finally, the results attained from the anthelmintic activity lowest time exhibited chloroform extract for paralysis and death.

25.3.2 Antispasmodic and Broncho Relaxant Activities

Aslam and Janbaz (2017) reported the crude aqueous-ethanol extract of aerial parts of plant *S. imbricata* and its sections in (0.01–10 mg/ml) collective conc. to perform the antispasmodic and broncho relaxant activities arbitrated by double Ca β 2 antagonistic and b adrenergic agonistic effects. The effect of crude extract on the preparation of jejunum with particular EC $_{50}$ values of 0.66(0.57–0.75), 0.69 (0.60–0.79) and 0.40 (0.35–0.46) mg/ml the crude extract potent effect, carbachol (1 μ M) and Kb (80 mM) brought retrenchments. It lifted Ca β 2 CRCs non-parallel way in rightward. The crude extract produced easing for the formation of tracheal isolation with EC $_{50}$ values of 0.74(0.66–0.84) and 0.86 (0.75–0.98) mg/ml and persuaded reduction Kp (80 mM) and carbachol (1 μ M). It showed carbachol CRCs destruction of highest reply with rightward. Before treatment in both tissues with (1 μ M) propranolol produced repressing CRCs in a right shift of extract in contrast to carbachol-induced contractions. Soothing smooth muscle shrinkages taken place along with ethyl acetate (EtOAc) fraction was more potent than the parental extract and its aqueous fraction.

25.3.3 Antibacterial Activities

Oueslati et al. (2017) analyzed the EtOAc extract of root and evaluated the two bioactive namely biphenylpropanoids (i) and biphenylsalsonoid (ii). These two compounds displayed significant antibacterial activity against three gram-positive and gram-negative bacterial strains. By using MIC values, both the compounds (i) and (ii) show the same activity against gram-positive and gram negative strains range from 16–32 mg/ml. The compound (ii) was found to be two times more active as compared to (i) against *M. luteus*. Due difference in structure biphenyl skeleton between two compounds, i.e., a new epoxy part at C-4 and another methoxy group at C-5. However, these two compounds showed some activity towards the tested bacteria except *M.*

luteus. Ajaib et al. (2020) reported 40 ± 1.5 mm zone of inhibition (ZI) against *Bacillus subtilis* in methanol extract of bark of *S. imbricata*.

25.3.4 Antioxidant Activities

Oueslati et al. (2017) evaluated the antioxidant activity by isolated two compounds (biphenylpropanoids (i) and biphenylsalsonoid (ii) from ethanolic root extract of *S. imbricata* and these compounds showed a modest antioxidant activity using DPPH• and ABTS•+ assays. The DPPH free radical scavenging with IC_{50} values of 122.3 ± 0.63 mg/ml and 86.5 ± 1.3 mg/ml and free radical scavenging capacity using ABTS•+ radical cation ($IC_{50} = 95 \pm 1.5$, 137.7 ± 1.2 mg/ml) respectively. The ABTS and DPPH free radical scavenging activities of compounds were similar. Due to the existence of two phenolic groups the compound (i) comparatively more active as compared to compound (ii) due to the presence of only one phenolic group.

Ahmed et al. (2008) showed the antioxidant activity of compounds 1–3 (Salsolins A (i) and B (ii), and 2 α ,3 β ,23,24-tetrahydroxyurs-12-en-28-oic acid (3) isolated from the *S. imbricata* and performed this activity by using DPPH scavenging assay. At the values of IC_{50} (20.4, 4.5 and 60.0 μ M,) compounds 1–3 was to be found, respectively, against as IC_{50} value of 44.2 μ M observed for butylated hydroxyanisole.

25.3.5 Anti-Inflammatory Activity

Osman et al. (2016) revealed isolated compounds and the total aqueous methanolic extract of leaves of *S. imbricata* were investigated by using the nitric oxides assay in RAW 264.7 macrophage cells at the concentrations 100 μ g/ml of all samples to performed *in vitro* anti-inflammatory action and reported distinct anti-inflammatory with non-toxicity of extracts.

25.3.6 Contraceptive Effect

Shehab and Abu-Gharbieh, (2014) investigated over a period of 65 days by oral management of the extract at two doses (250 and 500 mg/kg b. wt.) given in male rats to assess the contraceptive effect. In the hydrolyzed-methanolic extract of *S. imbricata* used to the estimation of a total of 13 and 8 components followed by HPLC analyzes. The total phenolic content was

conquered by quercitrin (12.692%) surveyed by coumaric acid (4.251%). Small weight of testis is caused by ethanolic extract by orally. The two treated groups, the amounts of sperm cells were decreased detected. High dose group was observed decreased in the epididymal sperm motility. The serum FSH, testosterone, and LH neither discrete change was noted. High range of these results supported in histopathological results. The male contraceptive activity of *S. imbricata* might be recognized to its phenolic gears, especially quercitrin.

KEYWORDS

- **Chenopodiaceae**
- **correlated spectroscopy**
- **heteronuclear multiple bond correlation**
- **heteronuclear single quantum correlation**
- **nuclear magnetic resonance**
- ***Salsola imbricata***

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CHAPTER 26

Biomolecules and Therapeutics of *Spathodea campanulata* P. Beauv.

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26.1 INTRODUCTION

Spathodea campanulata is called African tulip tree or Flame tree. It is a single species of the monotypic genus *Spathodea* in the flowering plant family Bignoniaceae with origin in Africa (Wagh et al., 2018). *S. campanulata* is commonly found in tropical and subtropical regions of Ghana, Nigeria, Uganda, Gabon, Cameroon, and Senegal. It is used for ornamental purposes and mainly used as folkloric medicine for series of diseases including infectious and metabolic disorders (Queiroz et al., 2014).

26.2 BIOACTIVES

Previous phytochemical studies related to *S. campanulata* have shown the occurrence of flavones, reducing sugars, carbohydrates, glycosides, alkaloids, terpenoids, and phenolic compounds (Dhanabalan, 2008a; Kumar and Thampi, 2015; Vastrad and Goudar, 2016; Zaheer et al., 2011). Unsaturated fatty acid, Oleic acid is present in flowers of *S. campanulata* (Goldson et al., 2016). GC-MS analysis evidence the presence of Butane, 1,1-diethoxy-3-methyl-, n-Hexadecanoic acid, 1,2-Benzenedicarboxylic acid, diisooctyl ester and oleic acid in *S. campanulata* flowers (Kumaresan et al., 2011).

The number of triterpenoids and steroid compounds were isolated and characterized from different parts of *S. campanulata* (Ngouela et al., 1988,1990, 1991). Spathoside is a cerebroside identified from the *S. campanulata* stem bark extract (Mbosso et al., 2008).

Several iridoid glycosides and iridoids were isolated from various parts of *S. campanulata*. They were characterized as spatheoside A, spatheoside B, spatheoside C, verminoside, catalpol, specioside, and ajugol (Gouda, 2009a; El Hela, 2001) and 6-O-Caffeoylcatalpol (Niyonzima et al., 1991).

A number of phenolic acids were reported from *S. campanulata*. The phenolic acids such as p-hydroxybenzoic, gallic, caffeic, protocatechuic, p-coumaric, chlorogenic, and ferulic acids (El Hela, 2001) and flavonoid type of compounds including naringenin, catechin-3-O- α -rhamnopyranoside, 5,6,4' trihydroxy flavonol-7-O- α -rhamnopyranoside (Shehab et al., 2014), quercetin 3- β -O-D-glucoside and quercetin 7-O- β -D-glucoside were also identified from *S. campanulata* (El Hela, 2001; Gouda, 2009b).

The chemical constituents of the essential oil from the *S. campanulata* flower was investigated by GC-MS. Total oil composition was 96.5%. 30 volatile compounds were identified including tricosane (3.7%), α -gurjunene (3.9%), aromadendrene (4.3%), farnesyl acetone (6.0%), α -humulene (12.7%) and benzyl benzoate (17.5%) as major constituents (Figures 26.1–26.4) (Villarreal et al., 2015).

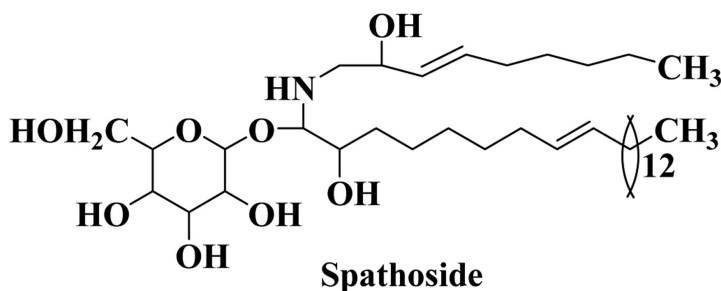


FIGURE 26.1 Cerebroside isolated from *S. campanulata* (Mbosso et al., 2008).

26.3 PHARMACOLOGY

26.3.1 Antioxidant Activity

Antioxidant capacity of the extract from *S. campanulata* aerial parts and purified compounds namely, ferulic acid, kaempferol 3-O-glucoside, caffeic

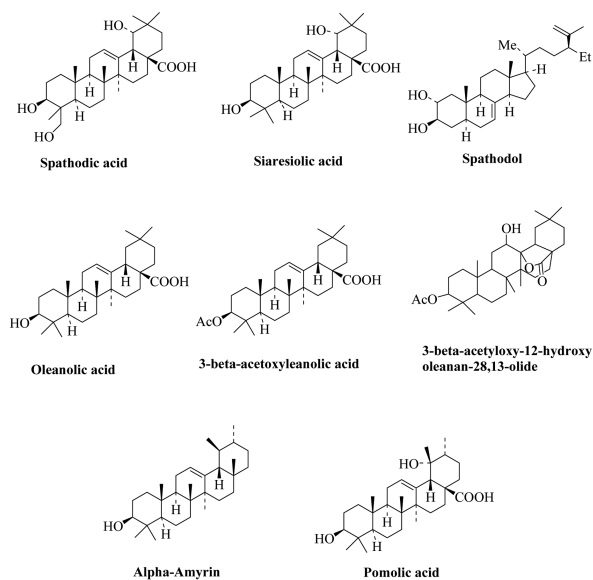


FIGURE 26.2 Terpenoids isolated from *S. campanulata* (Ngouela et al., 1988, 1990, 1991).

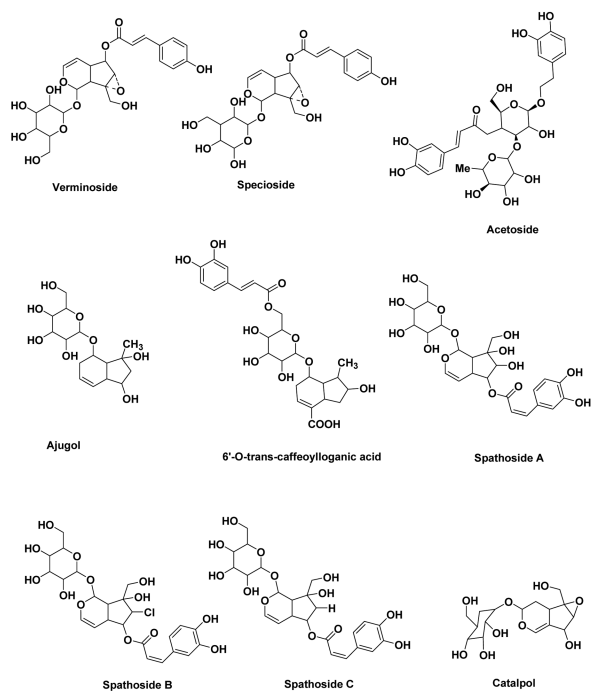


FIGURE 26.3 Iridoids isolated from *S. campanulata* (Gouda, 2009a; Niyonzima et al., 1991).

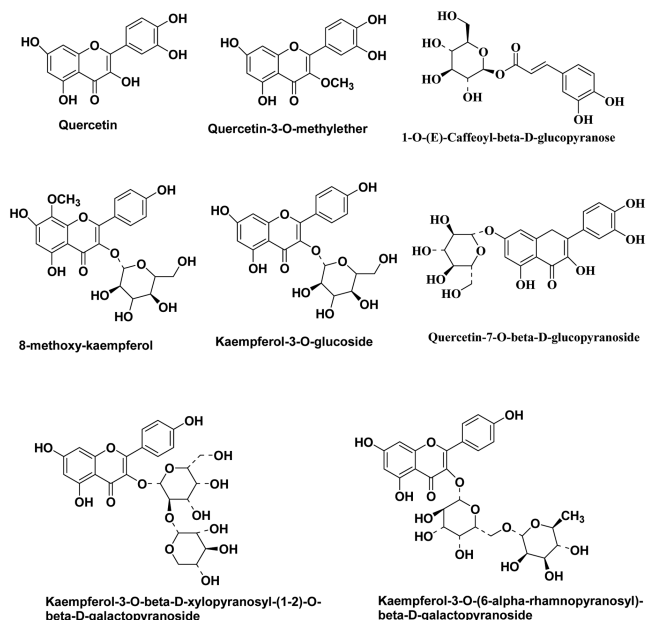


FIGURE 26.4 Flavonoids isolated from *S. campanulata* (Mbosso et al., 2008; Gouda, 2009b).

acid were reported to be significant (Nazif, 2007). Antioxidant constituents from *S. campanulata* contains verminoside (stem bark, leaf, flowers), specioside (flowers), kaempferol diglucoside (leaf), caffeic acid (leaf and fruits) were also reported (Elusiyan et al., 2011; Heim et al., 2012). DPPH radical scavenging potential and HPTLC fingerprint of methanol and aqueous leaf extracts were reported by Kulkarni et al. (2014). *In vitro* and *in vivo* antioxidant potential of *S. campanulata* leaf, flower extracts were evaluated by various chemical methods (Shanmukha et al., 2011; Coolborn et al., 2015; Santos et al., 2020).

26.3.2 Anti-Inflammatory Activity

Carrageenan-induced mice and rats were used to screen the *in vivo* anti-inflammation potential of *S. campanulata* leaf extract (Ilodigwe et al., 2010a). Another study evaluated the anti-inflammation efficiency of isolated compounds from *S. campanulata* were evaluated and reported that the compounds exhibit good anti-inflammatory activity (Boniface et al., 2014b).

26.3.3 Hypoglycemic, Anti-Complement, Anti-HIV Activities

The column chromatography fractions of *S. campanulata* stem bark decoctions were screened for Hypoglycemic, anti-complement, anti-HIV activities. Anti-HIV activity was evaluated on MT-4 cell lines using MTT assay (Niyonzima et al., 1999).

26.3.4 Anticonvulsant Activity

Crude ethanol extract and the isolated pure compound from the *S. campanulata* leaves were evaluated for anticonvulsant activity against chemically (pentylenetetrazole: PTZ) and electrically induced (Maximal Electro Shock) convulsion in mice. The crude extract and isolated compound showed significant abolition of PTZ and MES induced seizures (Ilodigwe et al., 2010b). Another study assessed the sedative and anxiolytic efficacy of *S. campanulata* leaf methanol extract based on its CNS effect by number of mice tests (Begum et al., 2020).

26.3.5 Hepatoprotective Activity

S. campanulata stem bark aqueous extract was screened for hepatoprotective and curative potential in hepatotoxic rats induced *via* carbon tetrachloride. In both studies, *S. campanulata* exhibited significant hepatoprotection against CCl₄ induced liver damage. These results were related to its antioxidant capacity and CYP 450 enzyme inhibition potential of *S. campanulata* which might be the reason for hepatocyte protection (Ansah et al., 2013).

26.3.6 Antimicrobial Activity

Stem bark extract of *S. campanulata* in methanol and ethanol solvents were potentially effective against the tested pathogens (Ofori-Kwakye et al., 2009). Watery fluid present at the floral base of *S. campanulata* displayed concentration dependent antimicrobial activity (Killedar et al., 2011). Purified compounds of the stem bark extract namely, spathoside, and *p*-hydroxybenzoic acid efficiently controlled the development of tested pathogens (Teinkela et al., 2016). *S. campanulata* leaf extract in petroleum ether and methanol

solvents showed good inhibition against *Klebsiella pneumoniae* bacterial strains (Dhanabalan, 2008b). UHPLC-HRMS analysis of crude and fractions of extract from *S. campanulata* barks were known to be effective against the growth of *Helicobacter pylori* (Ngameko et al., 2020). Flower and leaf extract of *S. campanulata* in ethanol solvent were assessed for antibacterial activity by disc diffusion method. Both *S. campanulata* extracts showed considerable activity over the tested microbes (Rajesh et al., 2010). Antifungal activity of the iridoid glycoside ajugol and two phenolic acids were isolated from the root peel ethanolic extract of *S. campanulata* was evaluated against fungus *Cladosporium herbarum*. The iridoid glycoside did not exhibit any antifungal activity while phenolic constituents displayed antifungal activity (Pianaro et al., 2007).

26.3.7 Antimalarial Activity

The antimalarial effect of *S. campanulata* leaf and stem bark extracts and their column chromatography fractions on *Plasmodium berghei* in mice was reported (Makindet et al., 1987, 1988, 1990). Ethanol extracts of *S. campanulata* and *Conyza sumatrensis* leaves suppress the parasitemia percentage in *P. berghei* affected mice model (Boniface et al., 2014a). New triterpenoid compounds obtained from *S. campanulata* stem bark named as 3 β -hydroxyurs-12-en-28-oic acid (ursolic acid) and its derivatives 3 β -hydroxyurs-12,19-dien-28-oic acid, 3 β ,20 β -dihydroxyurs-12-en-28-oic acid exhibited significant activity against *P. berghei*. This is the first report of ursolic acid as an antimalarial agent (Amusan et al., 1996).

26.3.8 Cytotoxicity Activity

In vitro cytotoxic activity of volatile constituents of *S. campanulata* buds and flowers against breast and colon carcinoma cell lines (MCF7, HCT116) were evaluated (Eid et al., 2014). In another study, the cytotoxic potential of *S. campanulata* methanol extract was evaluated against sensitive leukemia CCRF-CRM cell lines. The methanolic extract displayed IC₅₀ value below 80 μ g/ml (Victor et al., 2016). *S. campanulata* flower extracts and fractions exhibit *in vitro* antitumor activity against the tested breast and colon carcinoma cell lines (Shehab et al., 2014). Antioxidant correlated anticancer efficiency of *S. campanulata* leaf extracts were

evaluated against EAC cell lines. 70% ethanol extract with high level of total phenolic content exhibited significant activity against EAC cell lines (Sangeetha et al., 2016).

26.3.9 Anti-Cataract Activity

The fresh flower bud exudates of *S. campanulata* were evaluated against cataractogenesis using rat lenses. Evaluation of the occurrence of cataract by determining the level of non-enzymatic antioxidant parameters (total protein concentration, glutathione (GSH), malondialdehyde (MDA)), and enzymatic antioxidants (superoxide dismutase (SOD), catalase (CAT)) in rat lens homogenates. Flower bud exudates of *S. campanulata* displayed a dose related anti-cataract activity (Gbemisola et al., 2014).

26.3.10 Antidiabetic Activity

Antidiabetic potential of methanolic extract from stem bark of *S. campanulata* has been reported by Tanayen et al. (2016b). Methanolic extract was subjected to serial solvent fractionation with hexane, ethyl acetate (EtOAc), chloroform and its antidiabetic activity was evaluated using an improved method of oral glucose tolerance test. All three tested fractions have anti-hyperglycemic potential and the hexane fraction showed dose-dependent activity (Tanayen et al., 2016b). Hypoglycemic effect of *S. campanulata* bark decoction and its solvent fractions were evaluated in STZ induced diabetic mice. *S. campanulata* had hypoglycemic activity but not influenced in insulin levels (Niyonzima et al., 1990, 1993).

26.3.11 Anti-Solar Activity

The UV absorption ability of *S. campanulata* aqueous methanol extract has been investigated. Methanol extract displayed significant absorbance at 200–240 nm and good absorbance at 240–325 nm. The moderate absorbance was observed in the 310–340 nm range. These results inferred *S. campanulata* extract has an ability to absorb radiation in the entire UV range and proved its photoprotection ability (Patil et al., 2009).

26.3.12 Toxicological Studies

The toxicity profile of ethanol extract from *S. campanulata* leaves at acute and sub-chronic levels were evaluated in Wistar rats. Tested dose range (100–250 mg/kg) does not produce observable toxic effects. Medium value of LD₅₀ is more than 250 mg/kg (Coolborn et al., 2012). Tanayen et al. (2016a) reported toxicity of methanol extract from *S. campanulata* stem bark against rats and mice. Single dosage of *S. campanulata* found to be safe and prolonged use may cause hematological and hepatological injury (Tanayen et al., 2016a). Another study performed at the dose range over 1000–5000 mg/kg and 750–3000 mg/kg. Tested extract has the medium lethal dose value of 4466.84 mg/kg. Toxicity test revealed that maximum toxic dose was exceeds 5000 mg/kg (Ilodigwe et al., 2010c).

26.3.13 Cardioprotective Effects

The cardioprotective effect of *S. campanulata* stem bark extract in ethanol solvent has been reported with isoproterenol (ISO)-induced myocardial infarction in Wistar albino rats (Abubaker et al., 2012).

26.3.14 Larvicidal Activities

Larvicidal and mosquito repellency studies of ethanolic extracts of *S. campanulata* leaves at various concentrations were performed against *Anopheles stephensi* vector of malaria (Aarthi and Murugan, 2010). The efficiency of aqueous extract of *S. campanulata* leaves against the dengue vector *Aedes aegypti* was evaluated at the larval and pupal stage. *S. campanulata* had significant larvicidal, pupicidal activity along with morphogenetic effects (Saranya et al., 2013a, b).

26.3.15 Wound Healing Activity

Mensah et al. (2006) described that methanol extract of *S. campanulata* bark and *Commelina diffusa* may have wound-healing potential with respect to their antioxidant and antiseptic effect of its bioactive components. The response of *S. campanulata* stem bark on wounds was studied in Sprague Dawley rats. *S. campanulata* showed a complete wound contraction in

treated rats (Ofori-Kwakye et al., 2011). Ointment prepared from methanolic extract of *S. campanulata* bark alleviates the scratch damage in the burned part of the tested rat model (Sy et al., 2005).

26.3.16 Insecticidal Property

Trigo et al. (2010) investigated the insect mortality of *S. campanulata* flowers. Among the 445 flowers inspected, 345 dead insects were reported. The mucus on the buds of *S. campanulata* may “suffocate” insects and greatly reduce their survival rate.

KEYWORDS

- *Anopheles stephensi*
- Bignoniaceae
- chromatography
- antidiabetic activity
- pharmacology
- *Spathodea campanulata*

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Phytochemistry and Pharmacology of *Persea americana* Mill. (Family: Lauraceae): A Review

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27.1 INTRODUCTION

The avocado (*Persea americana* Mill.) is native to Mexico and Guatemala. The consumption of avocado fruit in this region dates at least since 8000–7000 BC (Gutiérrez and Villanueva, 2007). In 2018, the world's avocado production was around 6.4 million tons, being cultivated in 75 countries (FAOSTAT, 2020). It is expected that this production grows (García-Vargas et al., 2020).

Besides the use of the fruit as food, for the Aztec and Mayan indigenous people, avocado was an important healing source. The leaves were used against coughs and colds, to relieve diarrhea, improve menstruation flow, treat hypertension, etc. (Tcheghebe et al., 2016; Gutiérrez and Villanueva, 2007). At present, the leaves are still used for medicinal purposes worldwide, e.g., in Mexico, Ecuador, Caribbean islands,

Turkey, and Nigeria (Brai et al., 2014; Kendir and Koroğlu, 2018; Antia et al., 2005).

27.2 BIOACTIVES

Chemical screening of avocado leaves has revealed the presence of phenolic compounds in avocado leaves, including eugenol, syringic acid, vanillic acid, ferulic acid, epicatechin, epigallocatechin, apigenin, naringenin, and kaempferol (Obboh et al., 2014). In another work, the ethanol extract of avocado leaves has shown the presence of procyanidin B1 and C1 and a high number of flavonols, including mono-, di-, and tri-glycosylated forms of kaempferol and quercetin (Yamassaki et al., 2017) (Figure 27.1).

In the category of volatile compounds (essential oils), the most abundant compounds in avocado leaves are estragole, sabinene, and 1R- α -pinene (Granados-Echegoyen et al., 2015). Another terpene found in the avocado leaves is lupeol (Obboh et al., 2014) (Figure 27.2). The fatty acids derivatives (acetogenins) persin ((Z,Z)-1-acetoxy-2-hydroxy-4-oxo-heneicosa-12,15-diene) and (E,Z,Z)-1-acetoxy-2-hydroxy-4-oxo-heneicosa-5,12,15-triene were also isolated from avocado leaves (Domergue et al., 2000) (Figure 27.3).

Besides the presence of C₇ sugars, perseitol, and mannoheptulose (Pedreschi et al., 2019) (Figure 27.4), arabinogalactan-protein-rich fraction has been characterized in an aqueous leaves extract. It contained a (1 \rightarrow 3)-linked β -D-galactopyranose main chain, mainly substituted at O-6 by galactose and arabinose residues (Yamassaki et al., 2018).

27.3 PHARMACOLOGY

27.3.1 Antioxidant Properties

The aqueous extract from avocado leaves, containing mainly phenolic compounds, presented antioxidant potential by the inhibition of Fe²⁺- and sodium nitroprusside-induced thiobarbiturate reactive species production in rat brain homogenates, and radicals scavenging activity, including 1,1-diphenyl-2-picrylhydrazyl (DPPH), nitric oxide, and hydroxyl. The IC₅₀ values ranged from 2.05 mg/ml (NO radical) to 25.21 mg/ml (DPPH) (Obboh et al., 2016). In addition to phenolic compounds, C₇ sugars, and particularly mannoheptulose, also played an antioxidant role, especially in the fruit (Bertling et al., 2007).

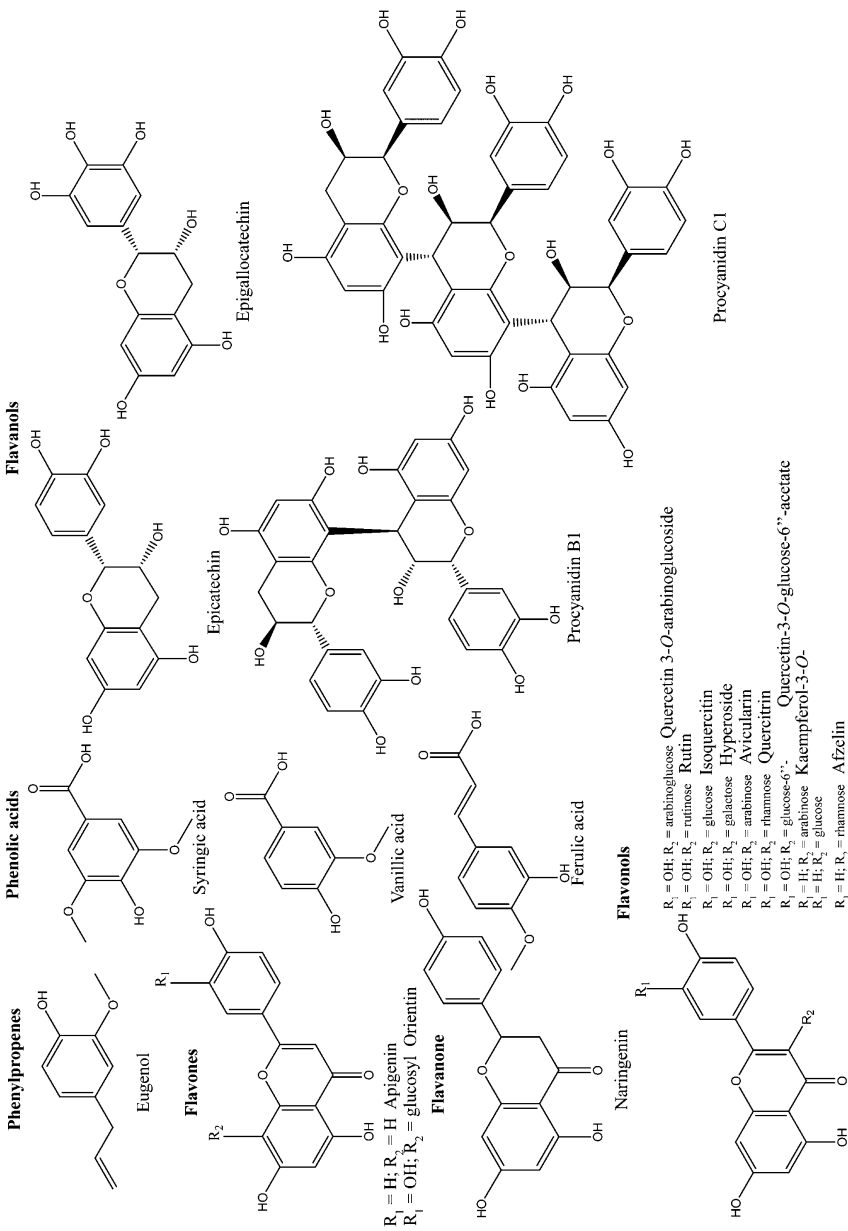


FIGURE 27.1 Chemical structure of phenolic compounds in avocado leaves (based on Domergue et al., 2000).

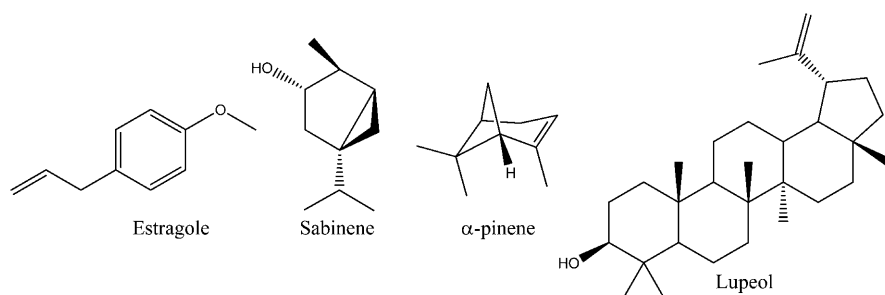


FIGURE 27.2 Chemical structure of some volatile compounds and triterpenes in avocado leaves (based on Granados-Echegoyen et al., 2015; Oboh et al., 2014).

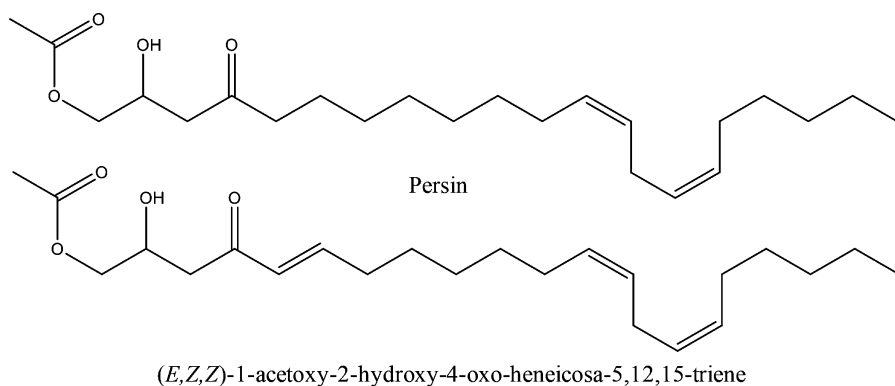


FIGURE 27.3 Chemical structure of some volatile compounds and triterpenes in avocado leaves (based on Domergue et al., 2000).

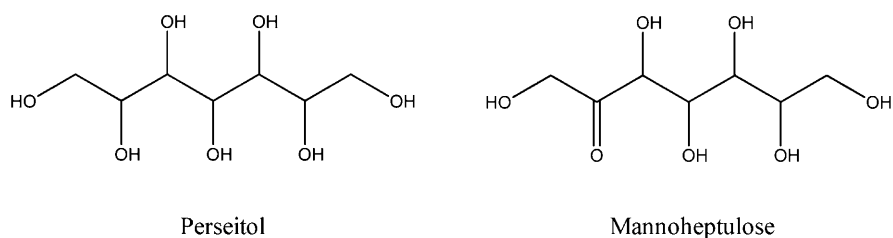


FIGURE 27.4 Chemical structure of C₇ sugars in avocado leaves (based on Pedreschi et al., 2019).

27.3.2 Antimicrobial Activity

Nathaniel et al. (2015) tested the antimicrobial activity of leaves extracts obtained by methanol, chloroform, ethyl acetate (EtOAc) and petroleum ether against the following microorganisms: *Bacillus subtilis*, *Escherichia coli*, *Salmonella typhi*, *Streptococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*. The solvent polarity index influenced the antibacterial activity of the leaves extracts, obtaining the highest antimicrobial activity using methanol as solvent with a minimum inhibitory concentration (MIC) from $1.56 \times 10^{-6}\%$ (*B. subtilis*) to 15.96% (*S. aureus*). Other biocompounds like persin and (*E,Z,Z*)-1-acetoxy-2-hydroxy-4-oxo-heneicosa-5,12,15-triene acted as an antifungal agent against *Colletotrichum gloeosporioides*, which causes avocado anthracnose (Domergue et al., 2000).

27.3.3 Analgesic and Anti-Inflammatory Effect

The aqueous extract of leaves has analgesic and anti-inflammatory properties that have been proven in mice by reducing the writhing induced by intraperitoneal injection of acetic acid, raising the heat pain threshold, and inhibiting formalin-induced pain. The extract also produced a dose-dependent inhibition of carrageenan-induced rat paw edema (Adeyemi et al., 2002; Kendir and K ro  lu, 2018). Different investigation showed that the leaves of avocado present anti-inflammatory effects due to the presence of flavonoids (Adeyemi et al., 2002; Arukwe et al., 2012).

27.3.4 Anticholinergic Properties/Anticonvulsant Activity

Aqueous and ethylic extracts of avocado leaves have effective anticholinergic properties *in vitro*, by blocking the action of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) enzymes, which catalyze the breakdown of choline esters (i.e., neurotransmitters) (Kose et al., 2020). Anti-cholinesterase activity has also been reported by Oboh et al. (2016).

Other authors have also revealed that the aqueous extract of avocado leaves (50–800 mg/kg i.p.) has anticonvulsant activity by reducing the convulsions induced in mice after the administration of pentylenetetrazole (PTZ) and picrotoxin. It was related to its ability to enhance neurotransmission in the brain (Ojewole and Amabeoku, 2006).

27.3.5 Anticancer Activity

Leaves contain persin, as commented before. Although it is toxic for some animals, persin is able to induce apoptosis in human breast cancer cells via arresting cells in G2M of the cell cycle and induce microtubule stabilization (Field et al., 2016). Roberts et al. (2007) also showed the efficacy of persin in estrogen receptor (ER)-negative (SK-Br3 cells) and ER-positive (MCF-7 and T-47D) breast cancer cells, both alone and in combination with 4-hydroxytamoxifen (4-OHT). For example, the IC_{50} of 4-OHT in MCF-7 and T-47D cells was reduced in the presence of persin (13.8 $\mu\text{mol/L}$), from 13.5 $\mu\text{mol/L}$ to 6.8 $\mu\text{mol/L}$ and 9.8 $\mu\text{mol/L}$, respectively. This suggested that it may act via an ER-independent mechanism. Moreover, the synergism was dependent on Bim expression. Alternatively, normal breast epithelial cells MCF-10A were not affected by persin.

27.3.6 Body Weight and Hyperlipidemia

The aqueous and methanolic leaves extracts (10 mg/kg body weight for 8 weeks) caused weight loss in rat models compared to hyperlipidemic controls. Apparently, the aqueous extract of leaves may increase lipid catabolism in adipose tissue (Brai et al., 2007). Moreover, in CCl_4 -intoxicated rats, an oral pre-treatment with aqueous extract of leaves (100 mg/kg/day and 200 mg/kg/day for 7 days) was able to reduce total cholesterol and triacylglycerols. The authors suggested that avocado leaves could protect against the development of fatty liver (Brai et al., 2020).

27.3.7 Urinary Tract Infections (UTI)

Leaves are widely used for pass kidney stones and against the urinary tract infections (UTIs) as a therapeutic agent among the people in Turkey and Cyprus (Kendir and K  ro  lu, 2018).

27.3.8 Antidiabetic Properties

Antia and co-workers (2005) have shown that the aqueous leaves extract of avocado possessed hypoglycemic effects in normal rats, thanks to the

reduction of blood glucose levels. Similar effects were observed for the hydroalcoholic extract from leaves (0.15–0.3 g/kg/day), which presented glycosylated flavonoids, when it was administered to streptozotocin (STZ)-induced diabetic rats. It could also regulate glucose in the liver and muscles through protein kinase B (PKB/Akt) (Lima et al., 2012). The study by Obod et al. (2014) also showed that the phenolic extracts of the avocado leaves could inhibit key enzymes linked to type 2 diabetes.

27.3.9 Hepatoprotective Activity

Different studies have been made to know the hepatoprotective activity of *P. americana* leaves. Results indicated that its methanol extract protects against paracetamol (PCM) induced hepatotoxicity (Ekor et al., 2006). Moreover, an oral pretreatment based on aqueous extract (100–200 mg/kg, 7 days) also showed significant protective effects against CCl₄-induced hepatotoxicity in rats; this effect appears to be dose-dependent (Brai et al., 2014). Both studies reported hepatoprotection effects are related to the antioxidant activity of avocado leaves.

27.3.10 Anti-Ulcer Activity

Investigations indicate that aqueous and methanolic extracts presents anti-ulcer activity. The aqueous leaves extract produced significant anti-ulcer dose-dependent activity when administered orally as a pretreatment to rats treated with the ulcerogenic drugs indomethacin and ethanol (Ukwe and Nwafor, 2004). Also, aqueous and methanolic extracts inhibited histamine-stimulated acid secretion via its action on H₂-receptors and produced anti-ulcer effects in male albino rats (Oluwole et al., 2011).

27.3.11 Immunomodulatory Properties

The arabinogalactan-protein-rich fraction exhibited *in vitro* immunomodulatory properties as an inhibitor of the classical pathway complement system via a hemolytic fixation test and comparing with heparin, which was used as a control for inhibition. With and without pre-incubation, the IC₅₀ values were 1.9 and 18.6 µg/mL, closer to the values obtained for heparin (Yamasaki et al., 2018).

27.3.12 Others

Avocado leaves essential oil has demonstrated larvicidal activity against the mosquito *Culex quinquefasciatus* (Say), the vector of various parasites, such as *Wuchereria bancrofti* (lymphatic filariasis) (Triteeraprapab et al., 2000). It inhibited the normal growth and development of mosquito larvae, as well as prolonged larval and pupal duration. Mortality was around 58% and 40% with the treatments of 800 g/mL and 50 mg/mL, respectively (Granados-Echegoyen et al., 2015).

KEYWORDS

- *Persea americana*
- 4-hydroxytamoxifen
- *Bacillus subtilis*
- epigallocatechin
- estrogen receptor
- protein kinase B

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CHAPTER 28

Bioactives and Pharmacology of *Olea europaea* L. (Family: Oleaceae)

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28.1 INTRODUCTION

The olive tree (*Olea europaea* L.) is one of the oldest known cultivated plants. Although it is native to the Mediterranean basin, its cultivation has spread globally during the past decades due to the high quality of the olive oil and the health properties attributed to its consumption. It has been estimated that in 2018, around 10.7 million hectares of olive trees were grown in 41 different countries (Contreras et al., 2020a). Besides olive oil, the interest in olive leaves has increased due to their pharmacology properties (Rahmanian et al., 2015; Talhaoui et al., 2015b). Today, leaves are currently key ingredients of dietary supplements, e.g., infusions, capsules, liquid solutions, etc.

28.2 BIOACTIVES

Chemical screening of olive leaves revealed the presence of a highly diverse phenolic class, including phenylethanoids as free forms and linked to secoiridoids and hydroxycinnamic acids, flavonols, flavones, and lignans (Figure 28.1) (Talhaoui et al., 2015a, b; Olmo-García et al., 2018; Medfai et al., 2020). Among them, oleuropein is generally the major compound and one of the responsible of the bioactive properties (Medfai et al., 2020). Other compounds characterized in leaves include free forms of secoiridoids, i.e., not linked to phenolic compounds (Figure 28.2) (Talhaoui et al., 2015a, b; Olmo-García et al., 2018; Taamalli et al., 2019).

In the category of volatile constituents, (*E*)-anethole, fenchone, and (*Z*)-3-nonen-1-ol (Figure 28.3) were found to be the main constituents of the oil volatile fraction from leaves of wild cultivars (Makowska-Wąs et al., 2017). Other major constituents found in Tunisia cultivars were (*E*)-3-hexanol, 3-ethenylpyridine, (*E*)- β -damascenone, and phenylethyl alcohol (Brahmi et al., 2012).

Other types of compounds in olive leaves extracts are triterpenoids, including uvaol, erythrodiol, oleanolic acid, maslinic acid, and ursolic acid (Martín-García et al., 2019; Taamalli et al., 2019) and the sugar alcohol mannitol (Contreras et al., 2020b; Lama-Muñoz et al., 2020a) (Figure 28.4). In addition to the phenolic compounds, the triterpenic acids oleanolic and maslinic acid, as well as mannitol are also of especial relevance from a pharmacological point of view (Contreras et al., 2020a; de la Torre et al., 2020).

The qualitative and quantitative composition depends on several factors, including the genotype, collecting period, conditioning treatment and the extraction method (Talhaoui et al., 2015a; Taamalli et al., 2019; Lama-Muñoz et al., 2020b; Medfai et al., 2020). For example, olive wild cultivars have shown a higher content of phenolic compounds, including oleuropein (Lama-Muñoz et al., 2020b).

28.3 PHARMACOLOGY

28.3.1 Antioxidant Properties

Aqueous alcoholic olive leaves extracts has shown antioxidant activity in *in vitro* assays, such as the ABTS and DPPH radical scavenging assays,

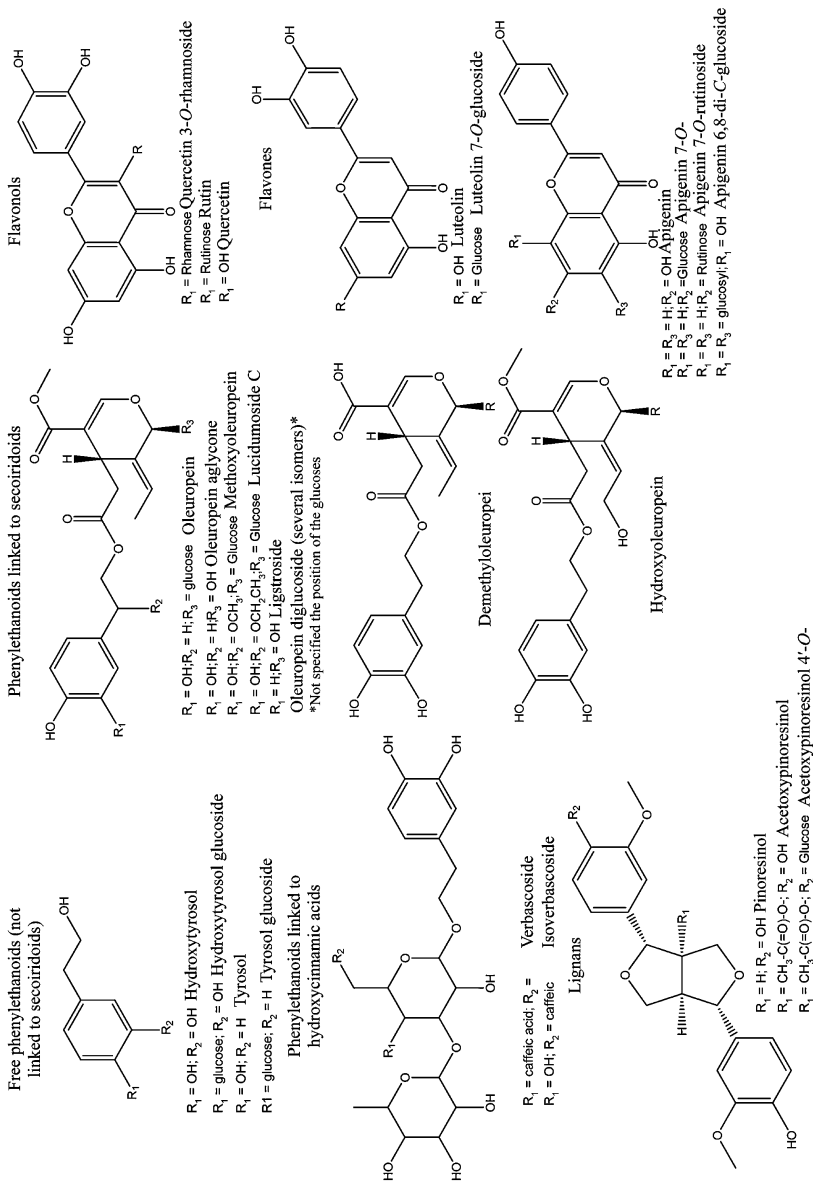


FIGURE 28.1 Chemical structure of phenolic compounds in olive leaves (based on Talhaoui et al., 2015b; Olmo-García et al., 2018; Taamalli et al., 2019; Medfai et al., 2020).

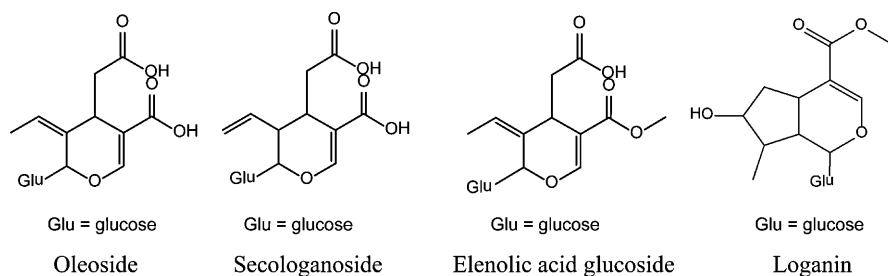


FIGURE 28.2 Chemical structure of secoiridoids (not linked to phenolic acids) in olive leaves (based on Talhaoui et al., 2015b; Olmo-García et al., 2018; Taamalli et al., 2019).

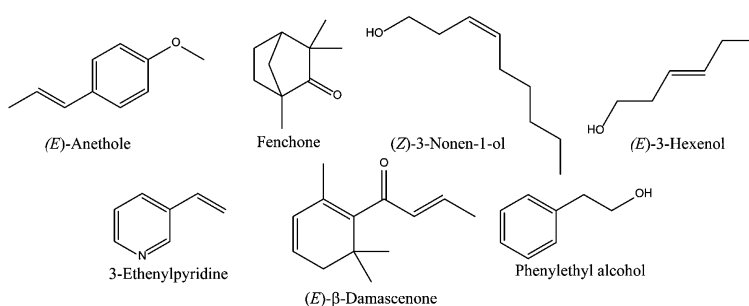


FIGURE 28.3 Chemical structure of main volatile compounds in olive leaves (based on Brahmi et al., 2012; Makowska-Wąs et al., 2017).

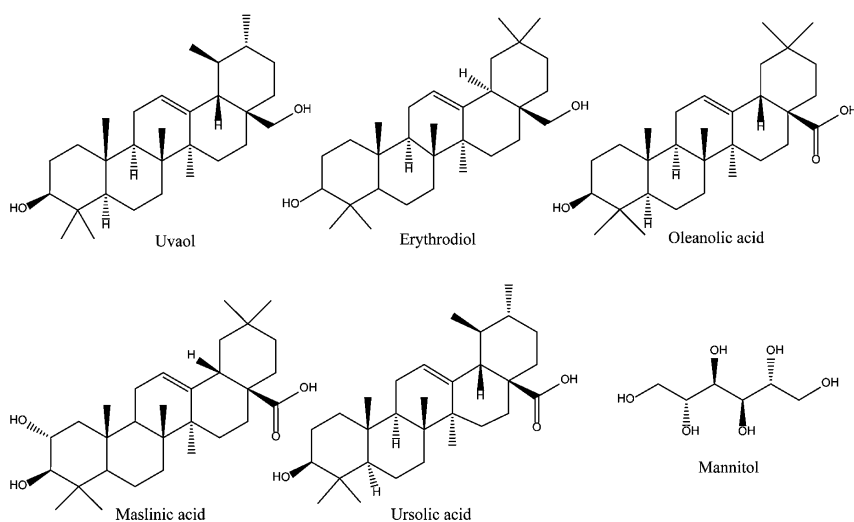


FIGURE 28.4 Chemical structure of triterpenoids and mannitol in olive leaves (based on Martín-García et al., 2019; Taamalli et al., 2019; Lama-Muñoz et al., 2020b).

ferric ion reducing antioxidant power, and oxygen radical absorbance capacity (Talhaoui et al., 2015b; Makowska-Wąs et al., 2017; Lama-Muñoz et al., 2019; Medfai et al., 2020), as well as it protected human erythrocytes against oxidative damage (Lins et al., 2018). In food systems, it also avoided lipid oxidation in meat systems with healthier lipid profile (Robert et al., 2019) and increased the antioxidant capacity of oils, its quality and oxidative stability (Şahin et al., 2017), especially, oleuropein contributed to this activity. It seems that aqueous ethanolic extracts has higher antioxidant activity than the volatile fractions, e.g., EC₅₀ values of 7.2–12.2 µg/mL vs. 2430–3471 µg/mL have been reported (Brahmi et al., 2012; Talhaoui et al., 2015b).

Moreover, among the bioactive compounds of olive leaves, hydroxytyrosol supplementation has shown a role in increasing endogenous antioxidants, particularly vitamin C, in clinical trial (Lopez-Huertas and Fonolla, 2017).

28.3.2 Antimicrobial Activity

The antimicrobial effect of different water extracts from olive leaves was investigated against human pathogenic bacteria and fungi. It was demonstrated that the extracts were effective against *Klebsiella* and *Pseudomonas*, two bacterial genera which pose a major resistance problem (Markín et al., 2003). Other genera are also susceptible, with minimum inhibitory concentration (MIC) values ranging from 70 µg/mL to 50 mg/mL, depending on the aforementioned factors and the bacteria (Brahmi et al., 2012; Rahmanian et al., 2015). Particularly, *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 27950 were highly susceptible to the volatile fraction of Neb jemel cultivar (Brahmi et al., 2012; Delgado-Adámez et al., 2016). Olive leaf extract have also showed antibacterial effects against foodborne bacteria: *Listeria innocua*, *Escherichia coli*, *E. coli* O157, and *Salmonella enterica*.

Muzzalupo et al. (2020) have demonstrated the *in vitro* antifungal activity of olive leaves (in a mixture of acetone and methanol (1:1, v/v)) against a *Fusarium proliferatum* AACC015. Other studies have revealed a higher antifungal efficacy for ethyl acetate (EtOAc), ethanol, and acetone extracts (MIC, 12–23 µg/ml) than the volatile fraction (MIC, not active-70 µg/ml) of the aqueous extract (not active), although the tested species were different (Korukluoglu et al., 2006; Brahmi et al., 2012).

28.3.3 Antiparasite Efficacy

Niazi et al. (2019) evaluated the scolicidal effects of olive leaves extracted with ethanol:water (70:30, v/v) on hydatid cyst protoscoleces from sheep livers *in vitro* and *ex vivo*. The mortality of protoscoleces was of 100% at 300 and 150 mg/ml, but it required a further time to display this effect.

28.3.4 Anti-Inflammatory and Anti-Atherosclerotic Effects

The aqueous-methanolic extract of olive leaves presented intestinal anti-inflammatory activity in two mice models of colitis, dinitrobenzene sulfonic acid (DNBS) and dextran sulfate sodium (DSS). It reduced the expression of proinflammatory mediators (interleukin-1 β , TNF- α , and iNOS) and improved the intestinal epithelial barrier integrity. These effects were also confirmed *in vitro* (Veza et al., 2017). In this regard, a clinical trial has shown that olive leaves extract can modulate vascular function and interleukin-8 (Lockyer et al., 2015).

The antiatherosclerotic effect of olive leaf extract has also been related to a suppression of the inflammatory response in rabbits with experimental atherosclerosis (Wang et al., 2008). Moreover, the supplementation with olive leaves extract (3%, for 8 weeks) attenuated the metabolic, structural, and functional changes in the heart in rats with a diet-induced metabolic syndrome, without changing blood pressure (BP). It was also related to a reversion of the chronic inflammation and oxidative stress (Poudyal et al., 2010). Oleuropein and hydroxytyrosol have been proposed as main active compounds (Efentakis et al., 2015). In fact, oleuropein (50 mg/kg) showed an anti-inflammatory effect against ischemia-reperfusion via decreasing the level of C-reactive protein *in vivo* (Nasrallah et al., 2020). Alternatively, hydroxytyrosol was able to modulate hepatic steatosis in a liver-on-a-chip model (Gori et al., 2020) and reduce systemic inflammation in children with pediatric non-alcoholic fatty liver disease at a dose of 3.75 mg of hydroxytyrosol plus 5 mg of vitamin E (Mosca et al., 2020). Verbascoside and maslinic acid can also have a protective anti-inflammatory role in olive leaves extracts according to other studies (Kostyuk et al., 2011; Georgiev et al., 2012; Zhang et al., 2020).

28.3.5 Blood Pressure (BP) Lowering Effects

In vivo, the antihypertensive effects of the consumption of oleuropein-enriched (15% w/w) olive leaves extract were demonstrated. It was related to the improvement of vascular function as a result of reduced pro-oxidative and

pro-inflammatory status (Romero et al., 2016). Moreover, in a recent clinical trial, pre 60 pre-hypertensive males were treated with olive leaves extract (136 mg oleuropein; 6 mg hydroxytyrosol) for six weeks. A BP-lowering effect (<4 mm Hg) and reductions in plasma total cholesterol, triglycerides, and in interleukin-8 were also observed (Lockyer et al., 2017).

28.3.6 Antidiabetic Effects

The efficacy of the oral consumption of olive leaves extract (500 mg/day in pill form) vs. a placebo equivalent to improve glucose homeostasis in adults with type 2 diabetes was studied. It improved glucose homeostasis in humans, and this effect was observed *in vivo* (Wainstein et al., 2012).

28.3.7 Bone Protecting Effects

In a recent clinical trial, the consumption of olive leaves extract and calcium (250 mg/day of olive extract and 1000 mg Ca) for 12 months was compared to the consumption of calcium alone. The former treatment increased the levels of the pro-osteoblastic marker osteocalcin and may stabilize lumbar spine bone mineral density. In addition, it improved the blood lipid profiles (Filip et al., 2015).

28.3.8 Anticancer Activity

Several studies in cells have shown the potential of olive leaves extract as an anticancer agent, e.g., against human embryo kidney cells (HEK293), human cervical cancer cells (Hela), ascites tumor cells (S180) and breast cancer cells JIMT-1 and MCF-7 (Bouallagui et al., 2011; Taamalli et al., 2012; Wang et al., 2018, 2019). One of the most susceptible cancerous cells were S180, in which the IC_{50} (50% effective concentration) was 457.69 $\mu\text{g/mL}$. It was observed an inhibition of proliferation through activation of caspase-3/9 and disruption of the mitochondrial membrane potential (Wang et al., 2019). Taamalli and co-workers found that ‘El Hor’ olive leaves extract, especially rich in luteolin and diosmetin, showed the highest cytotoxic activity against JIMT-1 (50% cytotoxic concentration of 7 $\mu\text{g/mL}$), by cell cycle arrest at G1 phase, which are partially mediated by ERK1/2 pathway inhibition (Taamalli et al., 2012; Barraji n-Catal n et al., 2015). Moreover, hydroxytyrosol rich

extract from olive leaves was able to promote cell cycle arrest in the G0/G1 phase in human breast cancer MCF-7 cells (Bouallagui et al., 2011). The cytotoxicity of oleuropein, hydroxytyrosol, tyrosol, and verbascoside towards cancer cells without affecting non-tumorigenic cells in cancers of the breast, prostate, and cancer have also been highlighted (Carrera-González et al., 2013; Zhou et al., 2014; Goldsmith et al., 2018). Also, triterpenic acids can have an implication in cancer prevention (Žibera et al., 2017).

KEYWORDS

- *Olea europaea*
- Olive
- human embryo kidney cells
- hydroxycinnamic acids
- minimum inhibitory concentration
- phenylethanoids

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CHAPTER 29

Biomolecules and Pharmacology of *Nepeta cataria* L. (Family: Lamiaceae)

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29.1 INTRODUCTION

Nepeta cataria or Catnip plant is a perennial herb found across the natural inhabitant regions in Europe, Asia, and Africa (Hatch, 1972). It belongs to the mint family, Lamiaceae, and is often found growing as herb or common garden plant up to a height of 25 to 40 cm. *N. cataria* has been used in traditional medicine due to its hallucinogenic activity in bringing a calming effect to patients facing mental disorders like hysteria and insanity or common problems like headaches (Grognet, 1990). The flowers and leaves of *N. cataria* are known to possess anti-spasmodic, antitussive or cough relieving, anti-flatulence, perspiration inducing, sedative, and emmenagogue properties (Adiguzel et al., 2009).

N. cataria has also been used traditionally to alleviate pain during toothaches or inflammation faced during hives as it brought an astringent effect on rubbing. It is widely used in food cuisines due to its minty lemony flavor. Beverages such as tea are also prepared using *N. cataria* due to its known benefits to cure hiccups in children, induce menstruation in women, assist parturition and relieve certain symptoms associated with respiratory disorders such as asthma (Grognet, 1990).

29.2 BIOACTIVES

The plants obtained from different places in the world show variations in the chemical composition of the constituent essential oils (Bourrel et al., 1993).

Serbian *N. cataria* essential oils obtained from its different plant parts have varied compositions. The floral essential oil predominantly contained sesquiterpenes (54.8%). The essential leaf oil is primarily composed of monoterpenes (54.6% to 94%), whereas stem oil is comprised of acids such as hexadecanoic and linolenic acids (39.3% and 31.4%, respectively). The most common monoterpene found was *cis*, *trans*-nepetalactone (29.1%) (Vukovic et al., 2016).

The Bulgarian population of *N. cataria* was reported to contain nepetalic acid, iridomyrmecin, isoiridodmyrmecin (structures shown in Figure 29.1), 4a, 7a-dihydro nepetalactone, as well as rare and unusual iridoids and alkaloids in their aerial parts (Handjieva et al., 1996). The essential oil obtained from *N. cataria* plants of Iran has been reported to contain isomeric nepetalactone as major components during vegetative, floral budding, and full flowering stages. Moreover, the full flowering stage compounds such as α -pinene (structure shown in Figure 29.2), β -pinene, nepetalactone were found in high amounts (Zomorodian et al., 2013).

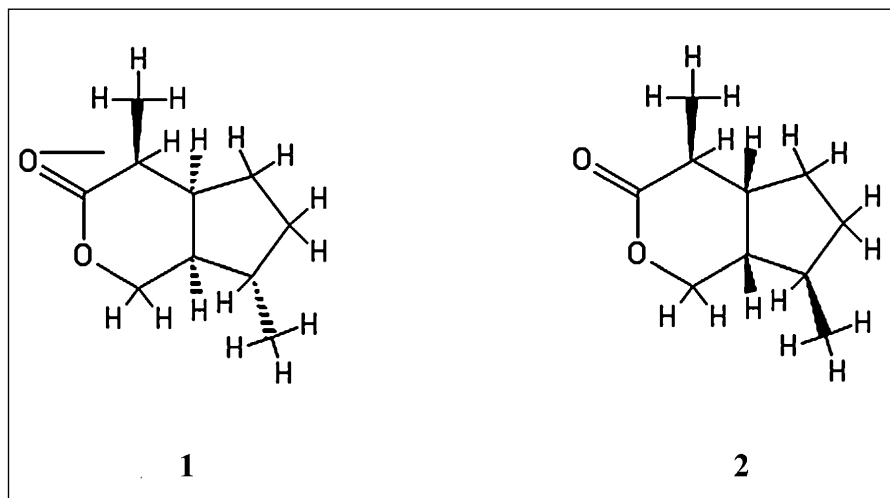


FIGURE 29.1 Chemical structures of some nepetalactones identified in *N. cataria*. (1) Iridomyrmecin (<https://pubchem.ncbi.nlm.nih.gov/compound/Iridomyrmecin>, 2D structure image of CID 442427 (iridomyrmecin)). (2) Isoiridomyrmecin (<https://pubchem.ncbi.nlm.nih.gov/compound/Isoiridomyrmecin>, 2D structure image of CID 120743 (isoiridomyrmecin)).

Argentinean catnip was found to consist mainly of nepetalactone and its dihydro form along with caryophyllene and its oxide (Malizia et al., 1996). The essential oil of *N. cataria* from France was reported to contain mainly

terpenoids like nerol and terpenoid aldehydes like geranial as its main constituents (Bourrel et al., 1993).

Oils obtained from flowering stage *N. cataria* plants grown in Lithuania were found to possess 71 constituents in its essential oil, with some been reported earlier. The most abundant components were sesquiterpenes like germacrene, caryophyllene oxide, and spathulenol. Other majorly found compounds were citronellal, geranyl acetate, citronellyl acetate (structures shown in Figure 29.2) and geraniol (Baranauskien et al., 2003).

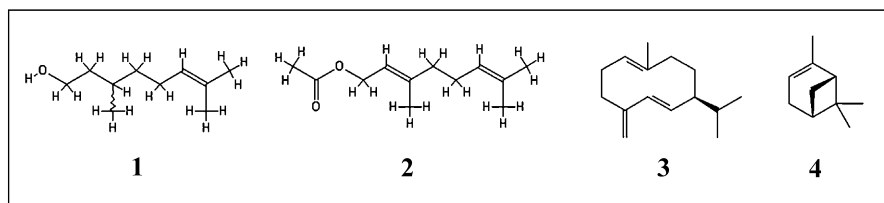


FIGURE 29.2 Chemical structures of some components identified in *N. cataria*. (1) citronellol (https://pubchem.ncbi.nlm.nih.gov/compound/3_7-dimethyloct-6-en-1-ol, 2D structure image of CID 8842 (citronellol)); (2) geranyl acetate (<https://pubchem.ncbi.nlm.nih.gov/compound/Geranyl-acetate>, 2D structure image of CID 1549026 (geranyl acetate)); (3) Germacrene (<https://pubchem.ncbi.nlm.nih.gov/substance/57389461>, 2D structure image of CID 57389461 (germacrene)); (4) α -pinene (<https://pubchem.ncbi.nlm.nih.gov/substance/8144374>, 2D structure image of CID 8144374 (α -pinene)).

According to an Iranian study, about 30 essential oil constituent compounds of *N. cataria* were identified as volatile and contributed to 99.7% of the essential oil composition. The grouping of contents in essential oil was reported and identified mainly as-monoterpene hydrocarbons 0.3%, oxygenated monoterpenes (98.1%), sesquiterpene, and sesquiterpenoids (0.9% and 0.2%) and other compounds (0.3%), with nepetalactone and its stereoisomers being the major oil constituents (Emami et al., 2016).

29.3 PHARMACOLOGY

29.3.1 Analgesic and Anti-Inflammatory Effect

N. cataria essential oil, when applied to mice in the edema test induced by carrageenan, showed an anti-inflammatory effect as it led to the decrease of edema with time. Both pain reflex tests and edema tests induced by carrageenan confirmed pain reduction and anti-inflammatory properties of the essential oil in mice. The tail immersion test in mice also revealed less potent but similar

central anti-nociceptive activity of essential oil to that of morphine, which remained up to 45 minutes since the administration of essential oil. Hence the major effects of essential oil on administration in mouse models indicated that it relieved pain through nervous system pathways (Ricci et al., 2010).

Calcineurin is an alkaline phosphatase (ALP) enzyme that regulates T-cell inflammatory genes, causing the production of interleukin (IL) and cytokines (Macleod et al., 2016; Medyouf et al., 2007). Binding of calmodulin to calcineurin increased its phosphatase activity by induction of conformational changes. According to Prescott et al. (2011), the extracts of *N. cataria* possess verbascoside and lamiuside A, which can directly interact and inhibit calcineurin in the presence or absence of calmodulin. This suggests that *N. cataria* possesses immunomodulatory properties.

29.3.2 Antimicrobial and Antioxidant Activity

The inhibitory capacity of *N. cataria* on bacterial enzymes such as thermonuclease, DNase, and lipase of certain *Staphylococcus aureus* strains was reported by using subminimum inhibitory concentrations ($\frac{1}{2}$ and $\frac{1}{4}$ MIC) of extracts obtained from the plant. Also, *N. cataria* was reported to be equally efficient in inhibiting enzymatic activities in both Methicillin-resistant *S. aureus* (MRSA) and Methicillin-sensitive *S. aureus* (MSSA) strains (Nostro et al., 2001). According to Zenasni et al. (2008), the essential oil of *N. cataria* possessed antimicrobial activity against *S. aureus*, *Escherichia coli*, and *Salmonella enteritidis* with *S. aureus* being more sensitive to the oil.

The essential oil of *N. cataria*, as well as its methanolic compounds, possessed different biological potential in totality against *Candida albicans* (yeast), different bacterial strains/ species like *Staphylococcus*, *Streptococcus*, *Proteus*, *Pseudomonas*, *Bacillus*, *Enterococcus*, *Escherichia*, *Brucella*, and *Acinetobacter* along with 15 fungal strains belonging to species of *Aspergillus*, *Fusarium*, *Monilia*, *Penicillium*, *Rhizopus*, *Rhizoctonia*, *Sclerotinia*, and *Trichophyton* (Adiguzel et al., 2009). Further, the study also revealed that the methanolic extract of *Nepeta cataria* possessed low antioxidant properties as it contained a lesser concentration of phenol contents.

Reports by Edewor and Usman (2011) highlighted the fact that *N. cataria* leaf extracts have antimicrobial activity against *Staphylococcus*, *Klebsiella*, *Salmonella typhi*, *Proteus*, *Streptococcus pyogenes*, *Shigella dysenteriae* and *E. coli*. The effect of these leaf extracts was found to be more pronounced against gram-positive than in gram-negative bacteria due to the structural differences of cell wall between the two bacteria types.

According to Bandh et al. (2011) *N. cataria* leaf extract showed potent antibacterial activity as compared to their antifungal functions. It was also reported to possess maximum inhibitory effect against *S. aureus* and *B. subtilis*, but mild activity against *A. flavus*. This study also highlighted that the effect of standard antibacterial compound streptomycin sulfate and antifungal agent nystatin was comparable to that produced by leaf extract of *N. cataria*.

29.3.3 Anticancer Property and Induction of Apoptosis

Apoptosis or programmed cell death is an essential process that checks the cell population in tissues (Elmore, 2007). The induction of apoptosis by plant extracts obtained from *N. cataria* was reported in prostate cancer cell lines like P53 and DU-145 as well as in breast cancer cell line MCF-7. The ethyl acetate (EtOAc) extract obtained from *N. cataria* enhanced the expression of a pro-apoptotic protein called Bax protein in P53 cells. The extract also cleaved caspase3 and poly-adenosine diphosphate ribose (PARP) to their active forms in a PC3 cell line that induced apoptosis (Emami et al., 2016).

The spread and growth of prostate and breast cancer has been reported to involve estrogens and their receptors (ERs) (De Mayo et al., 2002; Kuiper et al., 1996). *N. cataria* extracts (methanol, n-hexane, CH_2Cl_2 , EtOAc, n-butanol, H_2O compounds, and stereoisomers of nepetalactone (97.7%)) displayed more cytotoxic effect on estrogen-sensitive P53 cells in comparison to DU-145 cells which have less hormone receptors. The extract potentially contained β -sitosterol that mimics the function of estrogenic compounds that have steroidal structures. Hence the plant extracts of *N. cataria* can be used to check the progression and growth of breast and prostate cancers (Emami et al., 2016). Total flavonoid extract obtained from *N. cataria* (TFS) was found to disrupt the expression of micro-RNA (miR)-126 and regulate phosphatidylinositol 3-kinase/ protein kinase B (PI3K-Akt) pathway leading to anticancerous results in A549 cell line (Fan et al., 2017).

29.3.4 Anti-Diabetic Properties

The hypoglycemic efficiency of 70% ethyl alcohol extracts of *N. cataria* was investigated by Aly et al. (2010) in rat models. The study concluded that ethyl alcohol extracts could significantly decrease blood sugar levels, enhance carbohydrate hydrolyzing enzymes, and normalize liver function by

inhibiting diabetic complications such as lipid synthesis in mice. Therefore, the study indicated that *N. cataria* extracts could be used as natural anti-diabetic drugs.

29.3.5 Effects on Sexual Behavior

According to Hart et al. (1985), cats fed with catnip-stuffed toys showed different behavioral responses related to female sexual actions. Catnip evoked female sexual behavior in cats and other responses such as predatory, oral appetite, and play behavior. Male rats, when fed with chow rich in *N. cataria* leaves (10%), increased the penile erection (Bernardi et al., 2011) Also, *N. cataria* improved the sexual performance of male rats to a certain extent.

29.3.6 Effects on Central Nervous System (CNS)

According to Harney et al. (1978), catnip oil (500 mg/kg) significantly increased hexobarbital sleeping time in mice. *N. cataria* was reported to possess sleep-promoting properties (Fareed et al., 2013). The different dosage of alcoholic extract of *N. cataria* induced sleep in chicks in a dose-dependent manner.

Analysis with the help of various behavioral tests in male mice showed that persistent feeding of mice with chow containing *N. cataria* leaf extracts brought about an antidepressant effect (Bernardi et al., 2010). Apart from this, many other reports have directly used the anti-anxiety and antidepressant characteristics of *N. cataria* plant to treat stress, tension, and insomnia (Bhat and Moskovitz, 2009).

29.3.7 Hepatoprotective Effects

Drug-induced liver injury due to acetaminophen (APAP) or paracetamol (PCM) overdose causes liver oxidative stress, which is one of the leading liver problems. In mice models, the essential oils of *N. cataria* increased the mRNA expression by upregulating production of nuclear factor erythroid 2-related factor 2 (NRF-2). It is a transcription factor for enzymes, sulfo-transferase (SULT) and UDP-glucuronosyltransferase (UGT) that convert APAP to its non-toxic form. Along with this, the oil was also reported to

inhibit cytochrome P450 2E1 (CYP2E1) enzyme, hence leading to lesser production of the toxic intermediate, decreased concentration of APAP in plasma, indicating accelerated metabolism of APAP in a simple way (Tan et al., 2019).

29.3.8 Insect Repellent Property

The essential oil of *N. cataria* has been documented as a fly repellent against stable flies and houseflies. The repellence rates reported against *Stomoxys calcitrans* was greater than 96% at a dosage of 20 mg and was 86% for *Musca domestica* at a dosage of 2 mg (Zhu et al., 2009).

The essential oil of *N. cataria* on *Aedes aegypti* was found to be an effective repellent against mosquitoes. A time-course assay indicated that the essential oil was as effective as DEET (N, N-diethyl-3-methylbenzamide), a commonly used insect repellent, for the first two hours since its application (Reichert et al., 2019). The E, Z-isomer of nepetalactone, a component of *N. cataria* essential oil, was found to be more effective as an insect repellent than its other isomers (Peterson and Coats, 2001).

Topical application bioassay of essential oil of *N. cataria* showed high and low repellent activity compared to DEET against *Anopheles gambiae* and *Culex quinquefasciatus*, respectively. *N. cataria* extracts were also found to be repellent against brown ear ticks, *Rhipicephalus appendiculatus* and eco-parasitic red poultry mites, *Dermanyssus gallinae* (Birketta et al., 2011).

Evaluation tests of repellent behavior of essential oil of catnip against American cockroaches (*Periplaneta americana*) and houseflies (*Musca domestica*) revealed that it is a superior repellent in contrast to citronellal and DEET (Schultz et al., 2004). Additionally, it was also found that nepetalactone isomers and its racemic forms isolated from *Nepeta cataria* essential oil caused fewer mosquito bites of yellow fever mosquito (*Aedes aegypti*) when compared to repellents such as DEET and SS220 ((1S,2'S)-2-methyl pyridine-3-cyclohexene-1-carboxamide) against (Chauhan et al., 2005).

Amer and Mehlhoen (2006) evaluated catnip essential oil on human volunteers for its repellence capacity and protection potential against *A. aegypti*, *Anopheles stephensi*, and *Culex quinquefasciatus*. The oil successfully demonstrated a safety period of 8 hours, with 100% repellence efficiency for all three mosquito species studied.

29.3.9 Myorelaxant Activity

Gilani et al. (2009) found that *N. cataria* essential oil, verapamil, and papaverine subdued the unconstrained and excessive pre-contractions in rabbit jejunum. Thus *N. cataria* essential oil showed a spasmolytic effect, possibly by blocking the calcium channel. Also, *N. cataria* essential oil, papaverine, and verapamil brought about non-specific tracheal relaxation by the inhibition of the K⁺ induced contractions and carbachol (1 µM) in guinea pigs. The comparison between *N. cataria* oil and papaverine in bringing about the same level of non-specific tracheal relaxation indicated that *N. cataria* essential oil possessed similar phosphodiesterase inhibitor activity like that of papaverine. Further, in isolated guinea pig spontaneous beating atria, *N. cataria* oil brought cardio depression at a concentration 25–80 times more than that of equivalent papaverine.

Thus, the analysis highlighted that *N. cataria* possessed the myorelaxant and spasmolytic activities. It justifies the conventional application of *N. cataria* essential oil in cases of vomiting, cough, and diarrhea (Gilani et al., 2009).

KEYWORDS

- *Nepeta cataria*
- estrogens and their receptors
- ethyl acetate
- methicillin-sensitive *S. aureus*
- micro-RNA
- minimum inhibitory concentration
- sulfotransferase

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CHAPTER 30

Phytochemistry and Pharmacology of *Pancratium maritimum* L. (Family: Amaryllidaceae)

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30.1 INTRODUCTION

Pancratium maritimum L., also referred to as sea lily or sea daffodil, is a flowering species included in the Amaryllidaceae family, a monocotyledon group. Along the coastline of the Mediterranean region, *P. maritimum* is broadly distributed from the black sea to the Atlantic shore (Pouris and Rhizopoulou, 2018) with great esthetic value. Novel and unique bioactive compounds have been isolated from bulbous plants which are excellent sources of desirable pharmaceutical products for several medical applications (Hetta and Shafei, 2013). *P. maritimum* has attractive, delicate fragrant flowers appearing in late summers and usually leaves dry out before the flowering, appearing during hot summers. Plants are usually 30–70 cm long with umbel-shaped white large flowers with up to 15 cm long, including two third long corona and large bulbs with coastal habitat. Flowers appear in the month of June-September and are exposed to high temperatures, sea breeze, intense solar radiation, and water storage (Pouris and Rhizopoulou, 2018), possessing the property of drought resistance. *P. maitimum* is widely used as traditional medicine by various Mediterranean countries due to its remarkable pharmacological beneficial effects, as listed by Leporini et al. (2018).

30.2 BIOACTIVES

Structural alkaloids present in the Amaryllidaceae family have attracted substantial attention and have been included in the 20 most valuable alkaloids containing family isolated from the plants. *Pancratium* is derived from two Greek words, i.e., pan denoting all and cratos denoting potent (Gledhill, 2008). Bioactive metabolites detected from *P. maritimum* are listed in Table 30.1. Alkaloids detected from *P. maritimum* have diverse structural types, including tyramine, narciclasine, galanthamine, haemanthamine, lycorine, pancracine, tazettine, and homolycorine with prominent biological activities.

Several cytotoxic agents such as lycorine, tazettine, crinamine, and trispheridine have been isolated from *P. maritimum* exhibiting apoptosis and cytotoxicity whereas lycorine possessed antifungal activity (Hetta and Shafei, 2013). Lycorine alkaloid also has several activities such as anti-inflammatory, anti-viral, anti-tumor, and antiprotozoal (Bozkurt et al., 2019). Detected alkaloid galanthamine has highest acetylcholinesterase (AChE) enzyme inhibitory activity, and this metabolite is widely employed in Alzheimer's treatment (Figure 30.1) (Georgiev et al., 2011).

30.3 PHARMACOLOGY

30.3.1 Amoebicidal Activity

Ethanol extract of *P. maritimum* L. was effective against *Acanthamoeba castellanii* which causes amoebic keratitis causing a sight-threatening to the eyes. *P. maritimum* has an effective cysticidal effect at concentrations ranging from 20–0.02 mg/ml with a reduction in growth of *A. castellanii* by 34–94.3% by obtaining minimum inhibitory count 200 mg/ml at 72 hours (EI-Sayed et al., 2012). The reported activity may be due to the possible phenolics and flavonoids present in the plant.

30.3.2 Anti-Fungal Activity

Ethanol bulb extract of *P. maritimum* inhibited the growth of several yeast cultures at a concentration of 60 µg/disc. The extract inhibited the growth of *Candida pseudotropicalis* KUEN 1014, *C. krusei* ATCC 6285, *C. tropicalis* KUEN 1025, and *C. guillermundii* KUEN 998 with obtained zone of inhibitions (ZIs) 11 mm, 20 mm, 11 mm, and 26 mm (Sur-Altiner et al., 1999). Activity

TABLE 30.1 Bioactive Metabolites from *P. maritimum* L.

SL. No.	Part	Bioactives	References
1.	<i>P. maritimum</i> (Bulb)	Pancricin, pancrichromone, 2,4-dihydroxy-6-methoxy-3-methyl acetophenone, 5-formylfurfuryl acetate, 7-β-D-glucosyloxy-5-hydroxy-2-methylchromone, and ethyl-β-D-glucopyranoside	Ibrahim et al. (2014)
2.	<i>P. maritimum</i> (Bulb, leaves, flowers)	Trispheridine, Galanthamine, Buphanisine, Crinine, Haemanthamine, Tazettine, Lycorine, N-Formylgalanthamine,	Berkov et al. (2004)
3.	<i>P. maritimum</i> (Bulb)	Syzalterin (6,8-dimethyl-5,7,4-trihydroxyflavone), farrerol (8-dimethyl-5,7,4'-trihydroxyflava-none), liquiritigenin(4'-dihydroxyflavanone), isoliquiritigenin (4,2, '4'-trihydroxychalcone), Maritimin (7-hydroxy-5-methoxy-2-methylchromone), 2,4-Dihydroxy-6-methoxy-3-methylacetophenone, 2,6-Dimethoxy-4-hydroxyacetophenone	Youssef et al. (1998)
4.	<i>P. maritimum</i> (Fruits)	N-Formyl galanthamine, Galantamine, N-Demethyl galantamine, Buphanisine, Crinan-3-ol, Buphanidrine, Galanthane, Tazettine, Pancracine, Lycorine, Buphanamine, Anhydrolycorine, Crinamine, Crinane-3-one	Hetta and Shafei (2013)
	<i>P. maritimum</i> (Flowers)	Trispheridine, Galantamine, N-Demethyl galantamine, Crinan-3-ol, Tazettine, Pancracine, Lycorine, Crinamine	
5.	<i>P. maritimum</i> (cultivated shoots)	8-O-Demethylhomolycorine, N-Formylgalanthamine, Lycorine, 11-Hydroxyvittatine, Tazettine, Haemanthamine, Anhydrolycorine, Vittatine, N-Demethylgalanthamine, Buphanisine, Galanthamine, Trispheridine, Hordenine	Georgiev et al. (2011)
6.	<i>P. maritimum</i> (Bulb)	Hippeastrine, Demethylhomolycorine, Lycorine, Homolycorine, 11-Hydroxyvittatine, Pancracine, Tazettine, 11,12-Didehydroanhydrolycorine, O-Methylpretazettine isomer, Pancratinine C, O-Methylpretazettine, Assoanine, 2,11-Didehydro-2-dehydroxylycorine, Deoxytazettine, Galanthane, Demethylmaritidine, Galanthindole, Crinine, N-Demethyl galantamine, Buphanisine, Galanthamine, 5,6-Dihydrobicolorine, Trisphaeridine, Ismine, 1,12-Dehydrolycorene, 1-Acetyl-β-carboline, Hordenine	Bozkurt et al. (2019)
7.	<i>P. maritimum</i> (Bulb)	4'-Hydroxy-7-methoxyflavan, 4'-Hydroxy-5,7-dimethoxy-8-methylflavan, 5,7-Dihydroxy-6-methoxy-2,8-dimethylchromone, 5,7-Dihydroxy-2-methylchromone, 5-hydroxy-7-methoxy-2methylchromone	Ali et al. (1990)

TABLE 30.1 (Continued)

SL. No.	Part	Bioactives	References
8.	<i>P. maritimum</i> (Bulb)	Ferulic acid, 4-OH benzoic acid, vanillic acid, protocatechuic acid, syringic acid	Nikolova and Gevrenova (2005)
9.	<i>P. maritimum</i> (Leaves)	Coumaroyl quinic acid derivative I, coumaroyl quinic acid derivative II, caffeic acid-O-hexoside derivative II, ferulic acid-O-hexoside, quercetin tri-hexoside, quercetin pentose di-hexoside, quercetin di-hexoside I, quercetin di-hexoside II, Isorhamnetin di-hexoside I, Isorhamnetin di-hexoside II, quercetin pentoside-hexoside, Kaempferol pentoside-hexoside, quercetin hexoside I, quercetin hexoside II, isorhamnetin hexoside I, isorhamnetin hexoside II	Rokbeni et al. (2016)
	<i>P. maritimum</i> (Bulb scales)	Coumaroyl quinic acid derivative I, caffeic acid-O-hexoside derivative I, coumaroyl quinic acid derivative II, Isorhamnetin di-hexoside I, quercetin pentoside-hexoside	
	<i>P. maritimum</i> (Bulb tunics)	Quercetin pentose di-hexoside, quercetin di-hexoside II, Isorhamnetin di-hexoside I, quercetin pentoside-hexoside, Isorhamnetin pentoside-hexoside, quercetin hexoside II, isorhamnetin hexoside I, isorhamnetin glucuronide	
10.	<i>P. maritimum</i> (Flowers)	Lycorine, maritidine, lycoramine, galanthamine	Youssef and Frahm (1998)

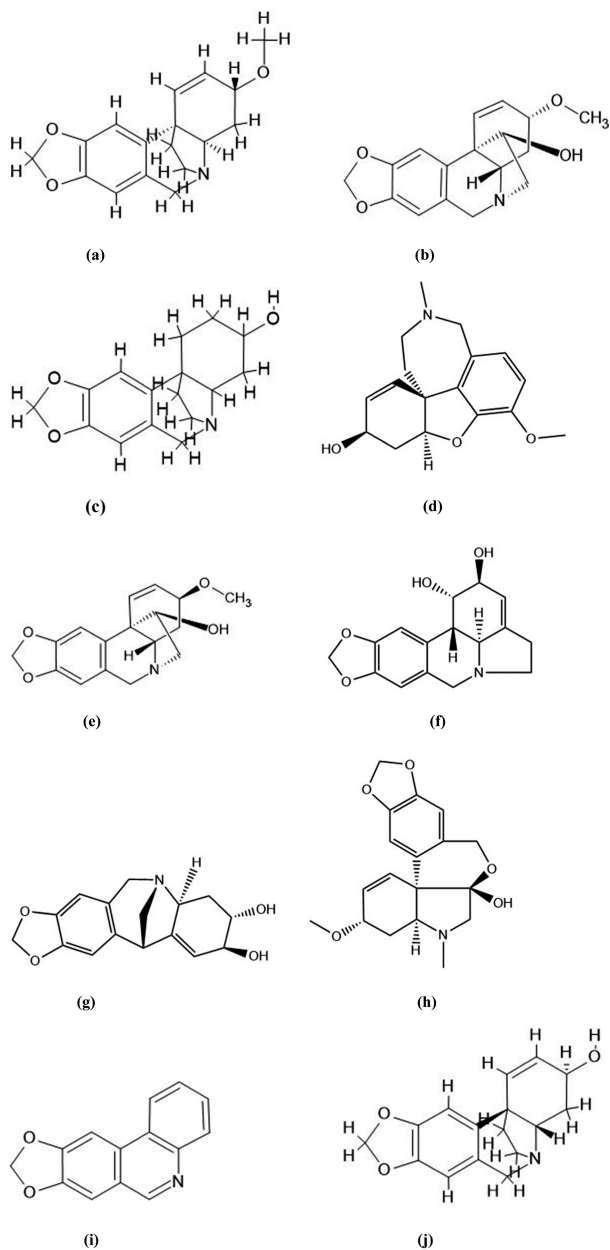


FIGURE 30.1 Structure of few compounds identified from *P. maritimum*: (a); buphanisine (b); crinamine (c); crinan-3- α -ol (d); galanthamine (e); haemanthamine (f); lycorine (g); pancracine (h); tazettine (i); trispheridine (j) vittatine.

was higher for *C. guillermondii* and *C. krusei*, followed by *C. pseudotropicalis* and *C. tropicalis*. The ethanolic flower extract inhibited *Aspergillus fumigatus*, *Trichophyton mentagrophytes* and *Rhizopus microsporus* with a minimum inhibitory concentration (MIC) 0.49 mg/ml, 0.98 mg/ml and 0.06 mg/ml (Nair and van Staden, 2017). Even, ethanolic flower and fruit extracts showed inhibitory actions against *C. glabrata* (RCMB 05274), *C. tropicalis* (RCMB 05039) having a ZI 13.9 ± 0.37 mm and 11.2 ± 0.58 mm for flower and fruit extract against *C. tropicalis* and for *C. glabrata* with 15.1 ± 0.25 mm and 14.6 ± 0.25 mm ZI (Hetta and Shafei, 2013).

30.3.3 Antibacterial Activity

The antibacterial activity was obtained against gram-positive bacteria *Streptococcus pneumonia* (RCMB 010010) with a ZI 16.9 ± 0.25 and 13.2 ± 0.58 mm for ethanolic extract of flower and fruits of *P. maritimum*. Even the activity was obtained against gram-negative bacteria *Klebsiella pneumoniae* (RCMB 0010093) and *Salmonella typhimurium* (RCMB 010072) for fruit and flower extract (Hetta and Shafei, 2013). The obtained activity was higher for flower extract in comparison with fruit extract. The activity was absent for *E. faecalis* for the ethanolic extract of fruit and flower.

30.3.4 Anti-Alzheimer's Activity

Flowers of *P. maritimum* extracted for crude alkaloid mixture possessed promising ability to inhibit AChE enzyme with obtained IC_{50} 22.02 ± 0.59 μ g/ml (Soltan et al., 2015). As it contains galanthamine and N-demethylgalanthamine alkaloids, which are potent inhibitors of AChE enzyme. Tazettine, galanthamine, and its derivatives, lycorine, crinine, and their derivatives were identified in the flowers. The obtained activity from flowers of *P. maritimum* is attributed due to the presence of some alkaloids especially galanthamine and lycorine derivatives by interacting synergistically with AChE. Bulbs were found to be more potent possessing ability to inhibit AChE enzyme with IC_{50} 3.49 μ g/ml and butyrylcholinesterase (BuChE) enzyme with 28.9 μ g/ml (Bozkurt et al., 2019). As both AChE and BuChE are responsible in AD by cleaving acetylcholine molecule and thus targeted therapy is to inhibit these enzymes, thereby elevating acetylcholine molecule level in the synaptic cleft. The obtained enzyme activity was higher for

AChE in comparison with BuChE. Shoots of *P. maritimum* cultivated under submerged conditions inhibited AChE with IC_{50} 6.12 $\mu\text{g/ml}$ intracellularly and extracellularly with obtained IC_{50} 289.5 $\mu\text{g/ml}$ at 35th day of cultivation. Considering this, the liquid culture of *P. maritimum* shoots would be the better option for producing molecules with AChE inhibitory potentials (Georgiev et al., 2011).

30.3.5 Cytotoxicity Studies

Flowers of *P. maritimum* showed a weak cytotoxic ability against the HepG2 cell line at concentration 5 $\mu\text{g/ml}$ and 200 $\mu\text{g/ml}$ (Soltan et al., 2015). Literature reports suggested that root, flower, and bulb extract have concentrations and time-dependent antiproliferative activity in MDA-MB-321 (Human breast cancer) cells by inhibiting cell growth and by blocking the cells at G2/M and S phase. The obtained IC_{50} values after 96 hours of incubation were 0.026 mg/ml for bulb extract, 0.03 mg/ml for root extract and 0.048 mg/ml for flower extract at the concentration of 0.1 mg/ml (Tayoub et al., 2018). Bulb extract demonstrated promising results in comparison with root and flower extracts. Ethanolic stem extract of *P. maritimum* showed favorable antiproliferative activity against C32 (*Amelanotic melanoma*) cell line with IC_{50} 27.1 $\mu\text{g/ml}$ and aqueous fruit extract against MCF-7 (human Caucasian breast carcinoma) cells with inhibitory concentration of 36.5 $\mu\text{g/ml}$ which inhibited 50% of cells (Leporini et al., 2018). Two extracted alkaloids Pancrimatine B and N-methyl-8, 9-methylenedioxyphenanthridine from *P. maritimum* have antiproliferative activity against the PC-3 cells (metastatic human prostate cancer cell line) (Ibrahim et al., 2013).

30.3.6 Antioxidant Activity

Antioxidant activity is mainly attributed due to the phenolics and flavonoid group present in the plant having the capacity to scavenge the damaging radicals. Antioxidant activity observed for *P. maritimum* was higher in the leaf region, followed by bulb tunics and bulb scales. The leaf extract showed 81.34% DPPH scavenging activity; this could be due to more phenolic content (Rokbeni et al., 2016). The activity was highest compared to bulbous parts as generally, the antioxidant ability is more in aerial parts compared to the bulbous parts. Even the ethanolic fruit extract, inhibited ABTS radicals

with an IC_{50} value of 6.9 $\mu\text{g/ml}$ and petroleum ether flower extract inhibited DPPH radicals with an IC_{50} value of 32.2 $\mu\text{g/ml}$ (Leporini et al., 2018). Flowers extract was also noted for the weaker antioxidant activity with less than 15% scavenging activity reported at the concentration of 100 $\mu\text{g/ml}$.

30.3.7 Prolyl Oligopeptidase Inhibitory Activity

Prolyl oligopeptidase is the cytosolic serine protease with overriding expression in the brain, with the shreds of evidence suggesting that it is involved in neuronal degeneration and aging. *P. maritimum* bulbs proved to have prolyl oligopeptidase inhibitory activity with inhibitory potential IC_{50} 78 $\mu\text{g/ml}$ compared to the standard (Z)-Pro-prolinal (Bozkurt et al., 2019).

30.3.8 Anti-Malarial Activity

P. maritimum showed good antimalarial activity against *Plasmodium falciparum* in a dose-dependent manner. This activity is due to the alkaloids containing tertiary nitrogen without methyl with methylene dioxybenzene part in the molecule providing higher activity. The *P. maritimum* L. extract showed antimalarial activity with IC_{50} obtained for chloroquine-sensitive (T9.96) with 1.56 $\mu\text{g/ml}$ and chloroquine-resistant (K1) with 1.83 $\mu\text{g/ml}$ strains of *Plasmodium falciparum* (Sener et al., 2003).

30.4 CONCLUSION

Bio actives present in different parts like bulb, flower, leaves of *P. maritimum* are the virtuous sources of desirable biological activities. Detected alkaloids consisted of medicinally important bio-actives with promising pharmacological properties can be effectively used to treat several diseases and ailments. Thus, the present chapter highlights the importance of bioactive metabolites present in *P. maritimum*. Hence, there is a necessity to increase the yield of metabolites following newer strategies. Clubbing of omics, bioinformatics, gene editing, and other molecular studies with the latest application of analytical instruments would assist in enhancing metabolite content in this and other medicinal plants. Gazing ahead, these efforts would yield lifesaving biomolecules in substantial quantities available to many populations.

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KEYWORDS

- *Acanthamoeba castellanii*
- acetylcholinesterase
- alkaloids
- Amaryllidaceae
- butyrylcholinesterase
- *Pancratium maritimum*

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Biomolecules and Pharmacology of *Hippophae rhamnoides* L. (Family: Elaeagnaceae)

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31.1 INTRODUCTION

Hippophae rhamnoides L., commonly known as sea buckthorn, is a deciduous flowering shrub in the family Elaeagnaceae. *H. rhamnoides* berries, known as ‘Drilbu’ and ‘Chharma’ in Himachal Pradesh, India. These berries possess the potential to remain intact throughout winter on the shrub, despite the coldest temperatures. Because of its high nutritive qualities, *H. rhamnoides* is domesticated and developed in plantations, particularly in Europe, China, Russia, Canada, and the USA, and is native to many other spots (Yang and Kallio, 2002; Panossian and Wagner, 2013). Numerous phenolic compounds in *H. rhamnoides*, including phenolic acids, flavonoids, and hydrolysable tannins, are liable for their bioactive and cancer-preventive properties. The composition of various parts of *H. rhamnoides* is firmly reliant on several factors such as variety, part of the plant, territory of development, organization

of soil, utilization of composts, and the level of maturity (Ciesarova et al., 2020). Due to its scientifically evaluated pharmacological properties *in vivo* and *in vitro*, it has been utilized as a traditional medicine for treating various diseases by folks' word wide (Patel et al., 2012; Chandra et al., 2018).

31.2 BIOACTIVES

Though *H. rhamnoides* is widely reported to be a prominent source of several bioactive compounds due to the presence of various phytochemicals, the specific cultivars considered is an important factor which affects the content and composition of *H. rhamnoides* plant parts. Considering the sugar content of the plant, a high amount of glucose is present compared to fructose, and very low levels of sucrose (Yang, 2009). *H. rhamnoides* is also found to be rich in proteins, free amino acids, lipids, and the oil content is abundant not only in the seeds but also in all the soft parts of the plant other than the leaves (Panossian and Wagner, 2013). Radenkovs et al. (2018) quantified and tentatively identified about 20 hydrophilic polyphenol compounds in the leaves and shoots of *H. rhamnoides*, including phenolic acids, flavonols, proanthocyanidins, and so on. The presence of polyphenolic acids like ferulic acid, hydroxycinnamic acid derivatives like p-coumaric acid fatty acids like palmitic acid, oleic acid, palmitoleic acid, and hydrolyzable tannins were identified in various parts of the plant, with the yield fractions varying based on the period of plant vegetation, period of harvesting, shoot length, etc. Some of the major polyphenols present in *H. rhamnoides* include about 25 flavonol glycosides from various parts of the plant consisting of quercetin-o-rhamnoside, quercetin-o-glucoside, quercetin-o-pentoxide, hydrophilic components like isorhamnetin, isorhamnetin-o-rutinoside I, kaempferol, and so on. Extracts of the leaves and berries revealed the presence of gallic acid, chlorogenic acid, caffeic acid, ferulic acid, rutin, luteolin, and carotenoid pigments such as lutein, zeaxanthin, xanthophyll, β -carotene, and β -cryptoxanthin (Panossian and Wagner, 2013). The ripe fruits primarily possess vitamin C and significant quantities of the vitamins E (tocopherols-mainly α -tocopherol and tocotrienols), F (α -linolenic acid and linoleic acid), K, and provitamin-A activity through the carotenoids (Criste et al., 2020; Ciesarová et al., 2020). Sterols like ergosterol, lanosterol, and some essential fatty acids were also found in nearly all parts of the plant (Wani et al., 2016). Figure 31.1 shows some of the structures of significant phytochemicals present in *H. rhamnoides* drawn using ACD/ChemSketch (version 2020.2.0).

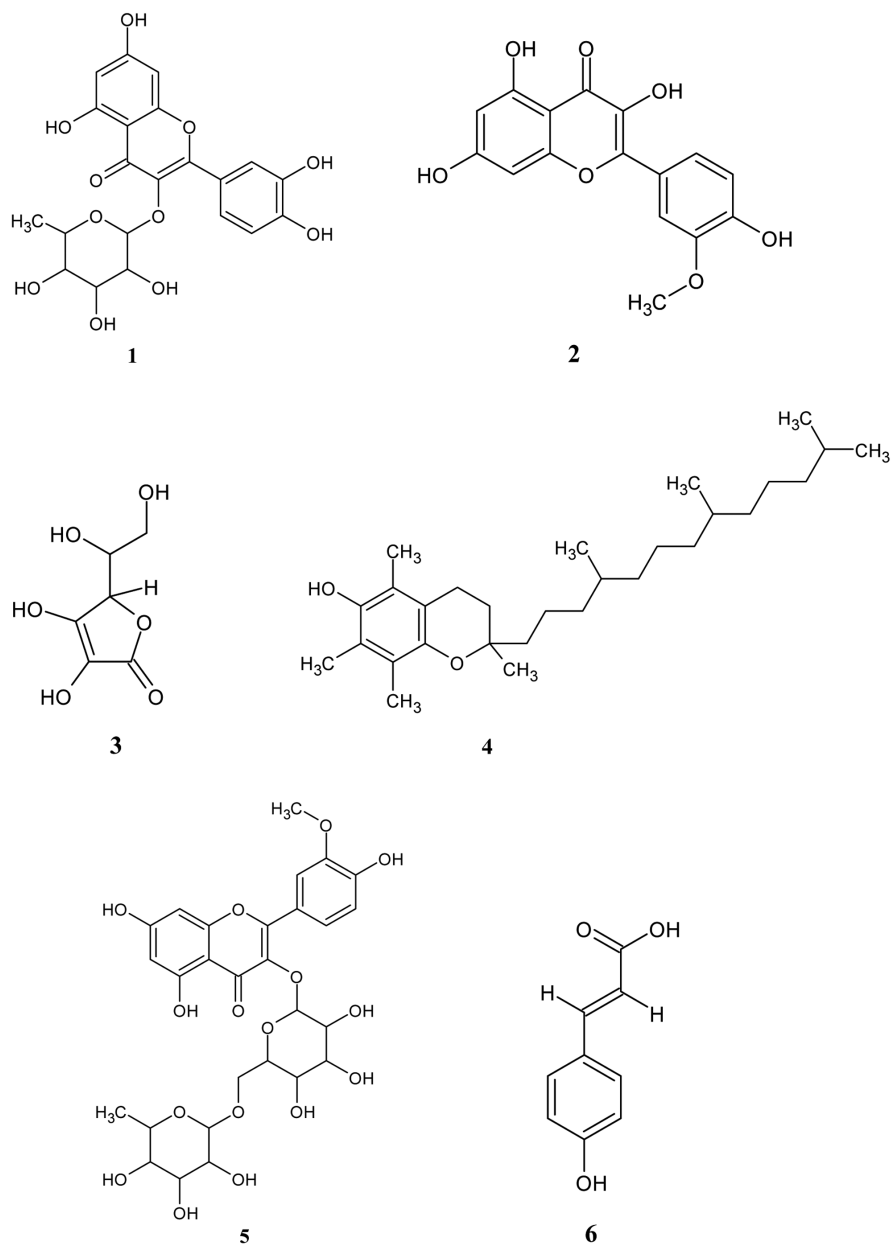


FIGURE 31.1 2D structures of quercetin-3-o-rhamnoside (PubChem CID 18604930) (1); isorhamnetin (PubChem CID 5281654) (2); vitamin C (PubChem CID 54670067) (3); vitamin E (PubChem CID 14985) (4); isorhamnetin-o-rutinoside (PubChem CID 5481663) (5); and p-coumaric acid (PubChem CID 637542) (6).

31.3 PHARMACOLOGY

31.3.1 Antioxidant Activity

Sytařová et al. (2020) study proved that both berries and leaves of *H. rhamnoides* are an excellent source of bioactive compounds, such as vitamin C, carotenoids, and phenolic compounds with a significant power of antioxidant activity. Great differences have been observed between the analyzed factors in various cultivars, in berries and leaves. Criste et al. (2020) concluded that specific varieties of *H. rhamnoides* and different parts of this plant can be used as potential sources of natural antioxidants and antimicrobials by using ethanol extracts of four cultivars of which three were homologated samples. Dienaitė et al. (2020) study proved that pressurized water extract of defatted *H. rhamnoides* pomace is abundant with a wide range of beneficial phytochemicals with antioxidant as well as anticancer activity. The extracted water fraction composed of 21 quantified phytochemicals, out of which tanshinlactone derivatives and galloylated flavanols play a pivotal role in the antioxidant and anticancer activities. Radulescu et al. (2019) analysis suggested that the highest antioxidant activity was recorded for the *H. rhamnoides* extract obtained by subcritical fluid method based on the high mass of flavonoids.

31.3.2 Antibacterial Activity

Phenolic rich fraction (PRF) from the leaves of *H. rhamnoides* prepared by sequential fractionation showed growth-inhibiting action against *Shigella dysenteriae*, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Salmonella typhi* (Kumar et al., 2013). Essential oils extracted from the seeds, pulps, and leaves of *H. rhamnoides* were obtained with hydrodistillation. The inhibitory effect of the oils from different parts of *H. rhamnoides* showed almost the same activity on *Staphylococcus aureus*. The most effective among these was the pulp oil, which exhibited antibacterial activity on all the bacterial species tested except for *E. coli*, for which the seed oil showed an inhibitory effect twice to that of the leaf or pulp oil (Yue et al., 2017). n-hexane and chloroform extracts of *H. rhamnoides* berries and n-hexane extract of leaves of the plant have antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Qadir et al., 2016). The antimicrobial activities of crude ethanolic extract from *H. rhamnoides* leaf, stem, root, and seed, and their respective fractions were obtained by liquid-liquid extraction using hexane, ethyl acetate (EtOAc) and water. The

study showed that the crude extracts were effective against gram negative and positive strains, and the root and seed extracts were better at radical scavenging than the stem and leaf extracts (Michel et al., 2012). Chae et al. (2012) evaluated the antibacterial activity and stability of a cream containing *H. rhamnoides* leaf extract. The minimum inhibitory concentration (MIC) values were obtained from the EtOAc fractions of *H. rhamnoides* leaf against *Escherichia coli*, *Pityrosporum ovale*, *Propionibacterium acnes* and *Staphylococcus aureus*. The results revealed that through the 12 weeks of the experimental period, no change in the color or smell of the cream was observed, and the cream with 0.25% EtOAc fraction of *H. rhamnoides* leaf extract was found to be stable.

31.3.3 Antifungal Activity

In the case of fungal cultures, among the test extracts used by Gupta et al. (2011), two compounds, fresh crude seed extract and concentrated crude seed extract showed significant activity against *Mucor* and *Tilletia* fungus. The methanolic-aqueous extracts of *H. rhamnoides* berries and leaves were tested for *in vitro* antifungal activity on *Aspergillus parasiticus* and *A. carbonarius* growth and they exhibited considerable effects (Roidaki et al., 2016). *H. rhamnoides* extracts demonstrated synergy with antifungal against *Candida albicans* by exhibiting an effect on yeast morphogenesis and biofilm formation (Sadowska et al., 2017).

31.3.4 Wound Healing Activity

Upadhyay et al. (2011) study indicated that wound healing activity in experimental burn wounds was promoted by the aqueous extract of *H. rhamnoides* leaf. A significant increase in the rate of wound contraction, the amount of hydroxyproline, hexosamine, and the protein contents demonstrated an inclined wound healing activity. The efficacy of *H. rhamnoides* seed oil while being tested on 5 adult sheep models subjected to third degree flame burns showed a very prominent wound healing activity in full-thickness burns and split-thickness harvested wounds (Ito et al., 2014). The effect of a polyvinyl alcohol-blended pectin hydrogel infused with the extracts of *H. rhamnoides* leaves on wound healing in a rat model was confirmed by histological evaluation of the wound tissue (Kim and Lee, 2017). The nanoemulsion gel formulation of *H. rhamnoides* seed oil showed better wound-healing,

antibacterial, and antifungal activity in comparison to pure *H. rhamnoides* seed oil (Kaur and Kapoor, 2018).

31.3.5 Anti-Inflammatory Activity

Immunomodulatory activity of *H. rhamnoides* leaf extract evaluated in adjuvant-induced arthritis (AIA) rat model by intraperitoneal administration resulted in observations suggesting significant anti-inflammatory activity and the potential for the treatment of arthritis (Ganju et al., 2005). In Rédei et al. (2018) experiment, the anti-inflammatory activity of the *H. rhamnoides* fruits was studied using *in vivo* rat paw edema models, which are standard models of mast cell degranulation-implicated inflammatory processes, and the inflammation-reducing activity of the 70% methanolic extract was confirmed in the 48/80-induced rat paw edema test. Tanwar et al. (2018) study was conducted to assess the immunomodulatory activities of phytoconstituents present in *H. rhamnoides* leaves. The parallel methanol fraction of the aqueous-alcoholic leaf extract significantly suppressed lipopolysaccharide-induced nitric oxide production and pro-inflammatory cytokines such as TNF- α , IL-6 and IFN- γ and also the inducible nitric oxide synthase and Cyclooxygenase-2 expressions. Balkrishna et al. (2019) performed the chemical analysis of *H. rhamnoides* oil and investigated its mechanism of action in its anti-inflammatory and anti-psoriasis-like activities in bacterial lipopolysaccharide-stimulated human monocyte (THP-1) cells under *in vitro* conditions and provided scientific evidence that the *H. rhamnoides* oil obtained from the pulp of the *H. rhamnoides* berries can be used as a therapeutic agent in subduing systemic inflammations and psoriasis-like lesions.

31.3.6 Antihyperglycemic Activity

Zhang et al. (2010) designed a study to investigate the antihyperglycemic activity of the aqueous extract of *H. rhamnoides* seed residues in streptozotocin (STZ) and high-fat diet (HFD)-induced type 2 diabetic rats and the results exhibited hypoglycemic and hypolipidemic effects in the STZ-HFD-induced type 2 diabetic rats. Sharma et al. (2011) also presented a study in STZ-nicotinamide induced type-2 diabetic rats to evaluate the antidiabetic and antioxidant activity of *H. rhamnoides* and similar results were obtained suggesting a protective effect on the animal model.

31.3.7 Antitumor Activity

Dienaitè et al. (2020) study proves *H. rhamnoides* pomace to be a rich source of potent phytochemicals exhibiting antioxidant and cancer cell proliferation inhibitory activities. This is especially observed in the case of the water extract, possessing a stronger antioxidant and growth inhibitory effect against HT29 and Caco-2 human epithelial colorectal adenocarcinoma cancer cell lines. Also, Masoodi et al. (2020) study concluded that *in vitro* prostate cancer proliferation was inhibited by the extract of *H. rhamnoides*. It effectively downregulated the androgen-responsive genes as well as the prostate specific antigen. Besides, a high-methoxyl pectin (HRWP-A) component separated from *H. rhamnoides* was claimed to possess antitumor activity against the Lewis lung carcinoma (LLC) growth in tumor-bearing mice and its potential as a new immuno-modulatory agent for cancer therapy (Wang et al., 2015). Another study on the growth and differentiation of cancer cells, the effects of ethanol extract from *H. rhamnoides* leaves on three acute myeloid leukemia cells, namely KG-1a, HL60, and U937 resulted in cell cycle downregulation and inducing apoptosis as well (Zhamanbaeva et al., 2014). When Grey et al. (2010) examined the antiproliferative effects of *H. rhamnoides*, the EtOAc extract gave the strongest inhibitory effect against Caco-2 cell line and ethanol: water extract gave a similar result in the case of HepG2 liver hepatocellular carcinoma cells.

31.3.8 Hepatoprotective Activity

PRF of *H. rhamnoides* pretreated rats 25, 50 and 75 mg/kg body weight when administered with CCl_4 showed reduced severity of liver intoxication, whereas the CCl_4 treated rats without PRF after 24 hours showed severe hepatocyte necrosis, fatty degeneration, vacuolation proving the hepatoprotective activity (Maheshwari et al., 2011). Hepatoprotective activity of *H. rhamnoides* oil against Aflatoxin B1 (AFB1) poisoning in chicken 6 days old was studied. The results showed that there was a decreased AFB1 accumulation in the liver tissues when treated with the *H. rhamnoides* oil. This potential hepatoprotective role was probably associated with the antioxidant components of the *H. rhamnoides* oil (Solcan et al., 2013).

31.3.9 Cardioprotective Activity

H. rhamnoides also owns its specialty in being an anti-cardiovascular medicine, decreasing cholesterol levels, and improving cardiac function. Atherogenesis

contributed by free radical-mediated oxidative processes is also alleviated by its antioxidant properties (Chandra et al., 2018). The total flavonoids of *H. rhamnoides* is also known to ameliorate mechano-cardiography and the ischemic electrocardiogram (Patel et al., 2012). Extracts from various parts of the plant were also found to be useful in treating coronary heart disease (CHD) (Wani et al., 2016).

31.3.10 Gastro-Intestinal Effects

H. rhamnoides increased gastric emptying and gastrointestinal digestive function in children with functional dyspepsia, apart from the levels of appetite factors, leptin, and neuropeptide Y contributing to their overall growth and development (Xiao et al., 2013). In Süleyman et al. (2001) study, *H. rhamnoides* exhibited beneficial effects on gastric tissue glutathione (GSH) levels and on the prevention of ethanol-induced ulcer formation in rats. Its oil and hexane extracts were also found to be efficient in treating gastric ulcers and in preventing gastric injuries, respectively (Chandra et al., 2018).

31.3.11 Skin Treatment

H. rhamnoides, being enriched with several polyunsaturated fatty acids, can nourish skin, heal wounds and treat other skin related diseases like eczema, chemical, and radiation caused epidermal burns, etc., when applied topically or taken orally (Chandra et al., 2018; Wani et al., 2016). When patients with skin burns are treatment with *H. rhamnoides* oil as one among the constituents of dressing, it exhibited better wound healing compared to the control. It was also suggested for treating Atopic Dermatitis, however, no experimental data proved it to be effective (Panossian and Wagner, 2013).

31.3.12 Adaptogenic Activity

Studies have reported that *H. rhamnoides* oil and leaves increases cold and stress tolerance, prevents the decrease of the activity of metabolic regulatory enzymes caused due to stress, aids in post-stress recovery and has also improved the physical performance in rats (Panossian and Wagner, 2013). However, significant treatment effects were not observed in rats with respect

to the physiological, hematological, and histopathological parameters with the oil and aqueous fruit extracts (Wani et al., 2016).

31.3.13 Insecticidal Activity

The crude leaves extract of *H. rhamnoides* in different solvents were tested for larval mortality against fourth instars of *Anopheles stephensi* and *Aedes aegypti* viz. vector mosquito species (Ahmed and Ali, 2013). The results suggest that *H. rhamnoides* leaves exhibited noteworthy activity and could be measured as an effective natural larvicidal means against vector mosquitoes. Herbal oil vapors from *H. rhamnoides* was tested for its toxicity against the adults of *Sitophilus granarius*, and the results revealed that the essential oil exerted a strongly toxic effect on *S. granaries* (Keszthelyi et al., 2017).

KEYWORDS

- adjuvant-induced arthritis
- *Hippophae rhamnoides*
- coronary heart disease
- anti-inflammatory activity
- Lewis lung carcinoma
- methicillin-resistant *Staphylococcus aureus*

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CHAPTER 32

Bioactives and Pharmacology of *Dysphania ambrosioides* (L.) Mosyakin & Clemants

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32.1 INTRODUCTION

Dysphania ambrosioides (L.) Mosyakin & Clemants (Syn. *Chenopodium ambrosioides* L.) is a pantropical medicinal plant of the family Chenopodiaceae native to tropical America. The plant is also known with many vernacular names such as Mexcian tea, American wormwood, Indian Goose-foot, Paico, and Epazote. Due to cultivation for medicinal purposes, it has become escaped and now generally naturalized and frequently introduced in tropical and sub-tropical areas of this planet and mostly found near dumpy, marshy areas and roadsides. It is profusely branched annual with lanceolated and elliptical leaves and erects ascending, aromatic stem; seeds horizontal, sometimes oblique and brown. In AJK *D. ambrosioides* is commonly called Gandibuti and is traditionally useful for constipation, vermifuge, and to rejuvenate wounds (Ajaib, 2012). *D. ambrosioides* contain flavonoids used for pharmacological activities such as antileishmanial, cancer chemoprevention, etc. (Patrício et al., 2008; Cruz et al., 2007). Flowers and leaves of this weed are used against treatment of menses regulation and syndromes and treat uterine hemorrhaging (Cruz et al., 2007). A detailed review on the phytoconstituents and ethnopharmacology of the genus *Chenopodium* was carried out by Kokanova-Nedialkova et al. (2009). Similarly, Yadav et al. (2007) reviewed the pharmacology of the genus *Chenopodium*.

32.2 BIOACTIVES

Oxalic, succinic acids and malic were identified in ethanolic and aqueous extracts of *D. ambrosioides* (Gupta et al., 1971). Leaves, bark, and fruits of *D. ambrosioides* produced (1.03%) of essential oils through hydrodistillation. 29 compounds were identified 96.37% of oil by using chromatographic procedure. The phytochemical studies of qualitative and quantitative results were recognized as α -terpinene, *p*-cymene, *p*-cymene ascaridol, limonene, and ascaridol by GC-MS (Cavalli et al., 2004; Ahmed, 2000).

Lawrence (1999) described several other major constituents in the essential oil: *p*-cymene, ascaridole, α -terpinene, α -phellandrene, pinocarvone, terpinene 4-yle acetate, limonene (Cavalli, 2002; Johnson and Croteau, 1984). Essential oil comprised chiefly of oxygenated monoterpenes and sesquiterpenes: *p*-cymene (12.94%), 4-carene (13.55%) and α -terpinene (61.04%). Several inconsequential composites were also determined such as ascaridole (0.4%), δ -3-carene (0.58%), *cis*-verbenol (0.49%), thymol (2.19%), limonene (0.79%), limonene dioxide (0.42%), thujanol (0.77%) (Boutkhil et al., 2009). In Figure 32.1 structures such as *p*-cymene (19.3%), *cis*-ascaridole (38.1%), and α -terpinene (13.2%), the major volatile constituents of essential oils (Almadiy, 2020) are given and in Figure 32.2 novel flavon glycoside isolated from the fruit of *D. ambrosioides* (Kamil et al., 1992) are given. Kaempferol was encountered in *D. ambrosioides* (Jain et al., 1990). Quercetin is ubiquitously present in aerial portions of *D. ambrosioides* (Bahrman et al., 1985; Jain et al., 1990). Isorhamnetin was found in the fruits of *D. ambrosioides* (Jain et al., 1990). Kaempferol glycosides have been reported from the aerial parts (Gohar and Elmazar, 1997) and leaves (Arisawa et al., 1971). Ambroside with four variants were isolated by Arisawa (Arisawa et al., 1971). Phytochemistry of vegetative parts of *D. ambrosioides* revealed the appearance of avenasterol and spinasterol (Salt and Adler, 1985).

Essential oil of vegetative and floral parts of *D. ambrosioides* using GC and GC/MS contain 95% of oil. The major constituent were α -terpinene (64%) (Gupta et al., 2000). Jardim et al. (2008) analyzed the components of essential oil of *D. ambrosioides* and reported 13 compounds out of which 90.4% total volatile oil. Singh et al. (2008) reported the phytoconstituents in *D. ambrosioides* essential oil in leaves (percentage): β -myrcene (1.3%), α -terpene (47.37%), *dl*-limonene (0.94%), β -phellandrene (0.11), *cis*- β -ocimene (*Z*) (0.72), γ -terpinene (1.56), *trans*- β -ocimene (0.23), *p*-cymene (25.77%), α -terpinolene (0.13), β -caryophyllene (0.77), *trans-p*-mentha-2,8-dien-1-ol (0.7), 1-[2-methyl-5(1-methylethenyl)cyclopentyl]-(1 α , 2 α , 5 β)-ethanone (0.16), citronellyl acetate (0.04), 3,4, epoxy-*p*-menthan-2-one

(0.07), γ -curcmene (0.11), pipeitone oxide (0.6), *cis*-ascaridole (14.75%), *trans*-*p*-mentha-1(7), 8-dien-2-ol (0.36), 3,7-dimethyl-2,6-octadien-1-ol (0.1), *trans*-ascaridole (4.46%) (Figure 32.4).

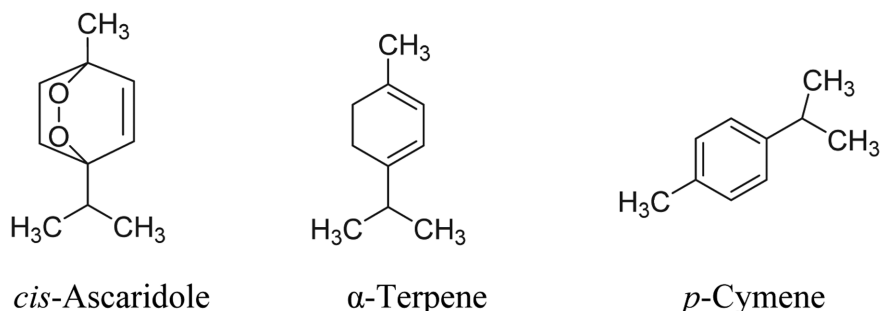


FIGURE 32.1 Major elements of *D. ambrosioides* crucial fats (Almadiy, 2020).

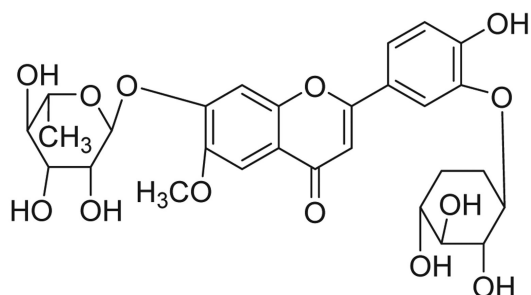


FIGURE 32.2 Flavon glycoside present in fruit of *D. ambrosioides* (Kamil et al., 1992).

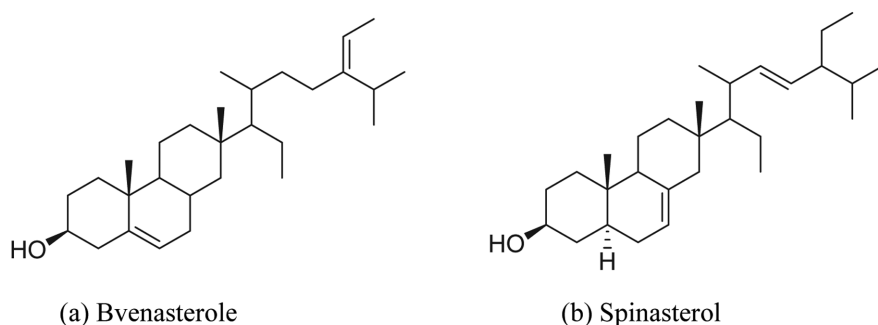


FIGURE 32.3 Phytosterols are present in leave and stem of *D. ambrosioides* (Salt and Adler, 1985). (a) Bvenasterole; (b) Spinasterol.

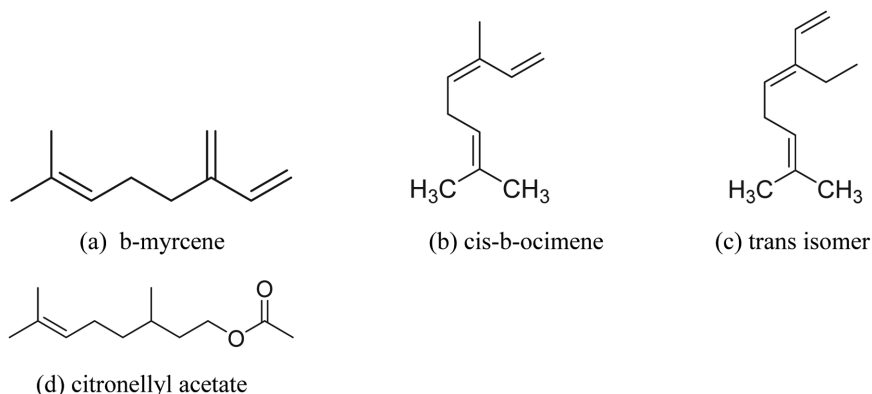


FIGURE 32.4 Three acyclic hydrocarbon monoterpenoid, and its composite isolated *D. ambrosioides* leaves (Singh et al., 2008). (a) b-myrcene; (b) cis-b-ocimene; (c) trans isomer; (d) citronellyl acetate.

D. ambrosioides essential oils from aerial parts were categorized into 66.9% oxygenated monoterpenes such as trans- and cis-ascaridole which are ingredients with 26.0% and 35.4%, correspondingly. Other trivial ingredients were trans- and cis-ascaridole glycol (1.7% and 2.1%, respectively) whereas secondary minor part of the oil contains p-cymene (29.2%) and monoterpene hydrocarbons (29.4%) (Pavela et al., 2017). Around 44 components were identified by El Mokni et al. (2019) in essential oil of *D. ambrosioides*, representing hydrodistilled oil (88.95%) and the most occurring ingredients were *cis*-ascaridole (60.33%).

Isomeric ($C_{10}H_{16}$) monoterpene like α -terpinene with its double bond's existence in positions 1 and 3 of the p-methane skeleton are given in Figure 32.1 (Almadiy, 2020; Araujo et al., 1996). The inflorescences of *D. ambrosioides* formed 1.3 mg/g¹ crucial fat (Juliana et al., 2015).

Phytosterols such as avenasterol and spinasterol present in leaves and stem of *D. ambrosioides* (Figure 32.3) (Salt and Adler, 1985). Two alcoholic structures of nerol (Chiasson, 2003) and geraniol (Omidbaigi et al., 2005) are present in *D. ambrosioides* oils (Figure 32.5). Other compounds isolated from aerial parts are given in Figure 32.6. Al-Kaf et al. (2016) reported that major compounds of essential oil were ascaridole (54.2%).

GC and GC/MS by Soares et al. (2017) investigated the monoterpenes *cis*-piperitone oxide (35.2%), *p*-cymene (14.5%), isoascaridole (14.1%), and α -terpinene (11.6%) as the major constituents of essential oil of *D. ambrosioides*.

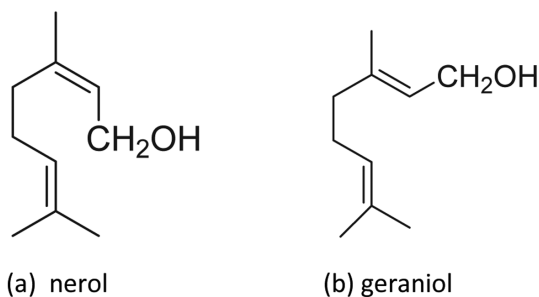


FIGURE 32.5 Two alcohols nerol (Chiasson, 2003) and geraniol (Omidbaigi et al., 2005) present in *D. ambrosioides* grease. (a) nerol; (b) geraniol.

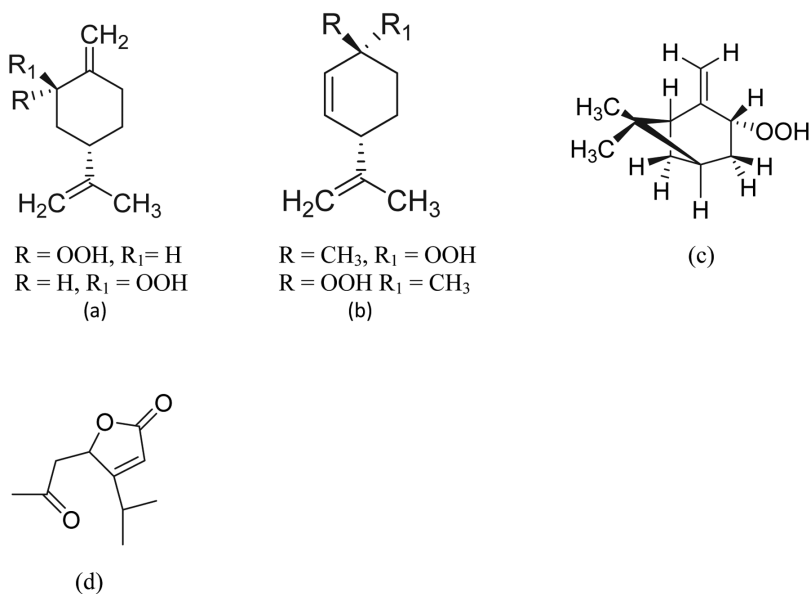


FIGURE 32.6 Four monoterpene hydroperoxides (a, b) (Kiuchi et al., 2002); and (c) *trans*-pinocarveylhydroperoxide (Okuyama et al., 1993); and (d) chenopanone isolated in the aerial parts of *C. ambrosioides* (Ahmed, 2000).

32.3 PHARMACOLOGY

32.3.1 Antimicrobial Activity

The aqueous and acetonetic extracts of aerial portions of *D. ambrosioides* have shown effects against the drug-resistant tuberculosis bacteria (CCK028469V) at fraction of 0.1 mg/mL (Lall and Leyer, 1999).

Antibacterial and antifungal potential of aqueous, essential oils and ethanol extracts of aerial portions of *D. ambrosioides* was assessed by Boutkhil et al. (2009) against one dozen microbes utilizing by disc-diffusion test where extracts tested showed no antimicrobial effect but essential oil inhibit the bacterial growth and fungi. In another study oil of *D. ambrosioides* revealed antimicrobial effects appeared against bacterial and fungal strains (Harraz et al., 2014).

Minimum inhibition concentration and zone of inhibition (ZI) methods used for the investigation of antimicrobial action against four bacterial and fungal strains were applied to assess the antimicrobial potential of *D. ambrosioides* (Ajaib et al., 2016). The essential oils containing α -terpinene contributed as major compound (54.09%) with effective antimicrobial activity against *S. aureus* (Bezerra et al., 2019). A weak activity is displayed by essential oil of *D. ambrosioides* against *Streptococcus sobrinus* MIC = 1000 μ g/ml (Soares et al., 2017).

The capsules containing essential oil of *D. ambrosioides* using one month showed an effective rate 95.26% in the treatment of peptic ulcer in China (Zhang et al., 2002). A new formulation of *D. ambrosioides* tested in treating peptic ulcer caused by *Helicobacter pylori* and found very effective treatment with lesser side effects and easily available raw material (Wei et al., 2007a, b). Ye et al. (2015) and Liu et al. (2013) also stated positive anti-*Helicobacter pylori* activity of *D. ambrosioides*. Owolabi et al. (2009) investigated the effective antimicrobial effects of essential oil of *D. ambrosioides* against all types of bacteria.

The essential oils extracted from the leaves possess a mild antimicrobial effect against *Staphylococcus aureus* (Alitonou et al., 2012). Shah (2014) and Jesus et al. (2018) evaluated crude methanolic extracts effective against human pathogenic bacteria *Escherichia coli* and *Klebsiella pneumoniae*.

32.3.2 Antioxidant Activity

C. ambrosioides extracts possesses equivalent effect compared to standard antioxidants and might be used in maintaining unsaturated compounds of industry and drug synthesis (Puhaca et al., 2000; Speisky et al., 2006). Three essential oils samples from *D. ambrosioides* were evaluated for determination of antiradical properties by Alitonou et al. (2012) and concluded that antiradical activity of crude extracts was 1000 times weaker than standard synthetic antiradical compound BHT. Ajaib et al. (2016) reported that

aqueous extract of fruit showed the highest percentage ($7.55 \pm 1.2\%$) of bound iron as juxtaposed to fruit extract of *D. ambrosioides*.

32.3.3 Amoebicidal Activity

In vitro antiamebic effects of *D. ambrosioides* basic oil revealed an $IC_{50} = 0.7$ mg/mL against trophozoites (Ávila-Blanco et al., 2014).

32.3.4 Insecticidal and Mosquitocidal Activity

D. ambrosioides essential oil displayed an important larvicidal potential against larvae of *Culex pipiens*, with low EC_{50} value (0.750 ppm) (Harraz et al., 2014) and similar results were also reported against *Musca domestica*, filariasis vector, housefly, and *Culex quinquefasciatus* (Pavela et al., 2017). Essential oils (EO) from *D. ambrosioides* more significant against *M. domestica* adults with LD90 assessed 99.5 µg/adult LD 50 as 51.7 µg/adult (Pavela, 2011). The vital oils and its fractions presented notable action against adults of *Culex quinquefasciatus* and third instar larvae and frictions of oils examined at 3.125, 6.25, 12.5, 25, and 50 µl/l dose depends death rate 80.11–100% and 91.22–100% is the adult and larval mortalities range at post-exposure for 24 h analyzed 50 µl/l, concentration. In the case of crude oil from *D. ambrosioides* strong adulticidal and larvicidal activities were noted (Almadiy, 2020). Larvicidal effect of the essential oil from the seeds were evaluated by Bigoga et al. (2013) against the larvae and adults of *Anopheles gambiae* mosquitoes and noticed that death rate of larvae take place at 300 ppm for the essential oils from seeds.

32.3.5 Schistosomicidal Activity

Kamel et al. (2011) reported that administration *D. ambrosioides* methanol extract (1250 mg/kg) to infected mice revealed a moderate antischistosomal potential. Continuous dosage give better results of antischistosomal properties and hence, enhanced the liver functions of subjected mice. *In vitro* schistosomicidal potential of *D. ambrosioides* essential oil (DA-EO) on *Schistosoma mansoni* was investigated by Soares et al. (2017). Dosage at 12.5 µg/ml possesses effective schistosomicidal potential and killed 100% of adult worms within 72 h.

32.3.6 *Myorelaxant Action*

D. ambrosioides essential oil (EODa) action as myorelaxant compound and its key component α -terpinene effective on isolated tracheal smooth muscle of rats (Pereira-de-Morais et al., 2020).

32.3.7 *Anti-Inflammatory Activity*

Dried leaves methanol extract of *D. ambrosioides* performed anti-inflammatory action. Extract (300–700 mg kg⁻¹, p.o.) dose formed associated to retard cotton pellet-made granuloma and carrageenan-brought paw edema in rats (Ibironke and Ajiboye, 2007; Trivellato-Grassi et al., 2013).

32.3.8 *Analgesic Effect*

At dose (300–700 mg kg⁻¹), *D. ambrosioides* methanolic extract performed analgesic action induced by formalin paw licking in rats through hot plate and early phase maintained at 55°C (Ibironke and Ajiboye, 2007). Aqueous extract of the leaf of *D. ambrosioides* has been evaluated by Amole et al. (2002) to determine analgesic effect on mice. Using the thermal (hot plate) test the plant extract was found effective at the dose of 0.4 g/kg and 0.8 g/kg in elevating pain threshold test. Antipyretic and analgesic effects of *D. ambrosioides* fresh leaf aqueous extract were investigated by Hallal et al. (2010) and concluded that extract possesses significant analgesic effect by reduction of writhing induced by acetic acid at dose of 300 mg/kg (p.o) in mice.

32.3.9 *Antineoplastic Activity*

Ascaridole isolated from *D. ambrosioides* essential oil used to perform antineoplastic activity against different tumor cells lines *in vitro* (MDA-MB-231, HL60, CCRF-CEM) (Efferth et al., 2002). *In vivo* condition *D. ambrosioides* leaves hydroalcoholic extract by, i.p. administration ascitic and solid Ehrlich inhibition were taking place. The treatment enhance the existence of tumor-bearing mice. Evidence indicates a small dosage and even two days after tumor establishment the *D. ambrosioides* has a strong anti-tumoral consequence (Nascimento et al., 2006; Hall, 2003).

The essential oil of *D. ambrosioides* reported to be effective against human breast cancer MCF-7 cells line. An inhibition was observed with IC_{50} values of 18.75, 9.45 and 10.50 $\mu\text{g/ml}$ at 6, 24 and 48 h, respectively (Wu et al., 2013). *D. ambrosioides*, commonly used in Portuguese folk medicine and methanolic extracts were used to evaluate antitumor and hepatotoxicity activities by Barros et al. (2013) and revealed that plant extract have anti-tumor effects against hepatocellular carcinoma cell lines.

32.3.10 Antiparasitic Activity

Leishmanicidal potential of an essential oil from *D. ambrosioides* against *Leishmania amazonensis* was evaluated and noticed that the tested product had a potential inhibitory activity against promastigote and amastigote forms, with ED_{50} value 4.6 $\mu\text{g/ml}$ (Monzote et al., 2006, 2007a, b, c, 2011, 2014). Ascaridole isolated from the aerial portions of *D. ambrosioides* were tested *in vitro* for trypanocidal activity against epimastigotes of *Trypanosoma cruzi* (Kiuchi et al., 2002). *D. ambrosioides* extracts of leaves were used in few villages near Tarapoto, San Martin to kill parasites and concluded to be effective 50% for *Ascaris* and 100% for *Ancylostoma*. The essential oil from *D. ambrosioides* revealed a significant effect against *Trichomonas vaginalis* with MIC of 25 mg/mL (Pollack et al., 1990; Giove, 1996; Monzote et al., 2004).

32.3.11 Anthelmintic Activity

D. ambrosioides studied as a vermifuge in lambs, testing both the essential oil and dried plant tissue and for this orally intake of the oil showed no toxic effects, although the active ingredient, ascaridole, was observed in the blood. A prominent reduction in the number of Trichostrongyle eggs per gram of feces was noticed in subjected lambs as juxtaposed with control lambs, but subjected lambs did continue to shed eggs in feces (Ketzi et al., 2000; Kato et al., 2008; MacDonald et al., 2004).

32.3.12 Immunomodulatory Effect

The protein-enriched fraction with crude extract of *D. ambrosioides* strongly stimulate murine but did no show any results on human lymphocytes (Rossi-Bergmann et al., 1997).

32.3.13 Cardiovascular Protective Properties

In a study, methanolic extract of *D. ambrosioides* leaves lowers blood pressure (BP) in rats and due to hypotensive effect may associate with cardiac effects (Assaidi et al., 2014).

32.3.14 Antipruritic and Antinociceptive Effect

The methanolic extract of *D. ambrosioides* leaves at 200 mg/kg (i.p.) produced an inhibition of the paw-edema induced by carrageenan in rats and a reduction in writhing induced by acetic acid in mice (Olajide et al., 1997).

KEYWORDS

- **carrageenan**
- **chemoprevention**
- **Chenopodiaceae**
- ***D. ambrosioides* essential oil**
- **monoterpenes**
- **phytosterols**

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