AAP Focus on Medicinal Plants Series

Phytochemistry and Pharmacology of Medicinal Plants

T. Pullaiah
Editor

CRC Press
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VOLUME 1

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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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About the Editor

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

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

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

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

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Abbreviations

ABTS	2,2-azino-bis-3-ethylbenzthiazoline-6-sulfonic acid
AC	asiaticoside
ACP	acid phosphatase
ACA	1′-acetoxychavicol acetate
ACA	A. caudatus agglutinin
ADA	adenosine deaminase activity
AE	aqueous extract
AETB	aqueous fruit pulp extract of T. bellirica
AF64A	ethyl choline aziridinium ion
AGEs	advanced glycation end products
AgNPs	silver nanoparticles
AI	atherogenic index
Akt	protein kinase B
ALP	alkaline phosphatase
ALT	alanine amino transferase
APC	amaranth protein concentrate
APH	amaranth protein hydrolysates
APTT	activated partial thromboplastin time
ARP	antiradical power
AST	amino transferase
AST	aspartate transaminase
AUUP	Amity University Uttar Pradesh
BAs	bile acids
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
BM HE-ext	hydroethanolic extract of Bacopa monnieri
BMOCs	bone marrow derived dendritic cells
BIC	biofilm inhibitory fixation
BuOH	butanolic fraction
bw	body weight
CAT	catalase
CCl4	carbon tetrachloride
CEBL	chloroform extract of leaves
CEO	*Cyperus esculentus* oil

CFA	Complete Freund's Adjuvant
CIA	collagen II-induced arthritis
CK-MB	creatine kinase-muscle/brain
CNS	central nervous system
COR-L23	lung carcinoma cell line
COX-2	cyclo-oxygenase-2
CS	cigarette smoke
Cyp2e1	Cytochrome P450 2e1
Cyp2f2	Cytochrome P450 2f2
DAF	defatted amaranth flour
DCM	dichloromethane
D-GaIN	D-galactosamine
DKA	ketoacidosis
DLA	Dalton's Lymphoma Ascitic
DMBA	7,12-dimethylbenz (a) anthracene
DMEM	Dulbecco's modified eagle's medium
DPPH	1,1-diphenyl-2-picrylhydrazyl
DTCE	defatted tubers of *Cyperus esculentus*
EAC	Ehrlich's ascites carcinoma
EAFWE	ethyl acetate fraction of water extract of C. *guaianensis* flowers
EETB	ethanolic residues of T. bellirica leaf
EHV-1	equine herpesvirus type-1
EO	essential oil
EPR	electron paramagnetic resonance spectroscopy
ESBL	extensive spectrum β-lactamase
EtOAc	ethylacetate
FBG	fasting blood glucose
FRAP	ferric reducing antioxidant power
FRSA	free radical scavenging action
FST	forced swim test
GC	gas chromatography
GPx	glutathione peroxidase
GSH	glutathione
GST	glutathione-s-transferase
HCA-7	human colon adenocarcinoma cell line
HDL	high-density lipoprotein
HEP2	human liver carcinoma cell lines
HIV	human immunodeficiency virus
HIF-1	hypoxia-inducible factor 1

HLPC-DAD	high-performance liquid chromatography
HMGR	hydroxymethylglutarate-coenzyme A reductase
HPDE-6	human pancreatic ductal epithelial
HPLC	high-pressure liquid chromatography
HPTLC	high-performance thin layer chromatography
HRBC	human red blood cell
Hela	cervical cancer cell line
HeLa cells	human cervical cancer cell line
HepG2	liver cancer cell line
HSF	human skin fibroblast
HSV	herpes simplex virus
HSV-1	herpes simplex virus type 1
H1N1	Influenza A
IC50	inhibitory concentration
IL	interleukins
IL-1β	interleukin-β
IL-6	interleukin-6
iNOS	inhibition of enzymes
iNOS	inducible nitric oxide synthase
IR	insulin struggle
IR	inhibition rate
K1	chloroquine-resistant
LCAT	lecithin-cholesterol acyltransferase
LC–MS	liquid chromatography–mass spectrometry
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LPO	lipid peroxide
LPS	lipopolysaccharide
MABA	microplate alamar blue assay
MCF-7	Michigan Cancer Foundation-7
MDA	malondialdehyde
MDA-MB-231	breast cancer cell lines
MDR	multidrug-resistant
MES	maximal electroshock stimulation
MeTB	methanolic residues
MIC	minimum inhibitory concentration
MMP	matrix metalloproteinase
MNCC	maximum noncytotoxic concentration
MPO	myeloperoxidase
MRC-5	lung fibroblast cell

MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
MTCC-441	*Bacillus subtilis*
MTCC-443	Escherichia coli
MTCC-737	*Staphylococcus aureus*
MTCC-741	*Pseudomonas aeruginosa*
MTT	3-(4, 5-dimethyl thiazol-2yl)-2, 5-diphenyl tetrazolium bromide
MTX	methotrexate
NDEA	N-nitrosodiethylamine
NFkB	nuclear factor kappa B
NIQ	dimeric naphthylisoquinolines
NK	natural killer
NO	nitric oxide
NPD	nitrophenylenediamine
NRU	neutral red uptake
OGTT	oral glucose tolerance test
ORAC	oxygen radical absorbance capacity
PBMCs	peripheral blood mononuclear cells
PC-3	prostate cancer
PGE2	prostaglandin E2
PPARα and PPARγ	peroxisome proliferator-activated receptors
PPOs	polyphenol oxidases
PT	prothrombin time
PTZ	pentylenetetrazole
RBC	red blood cells
RBEF	Ritnand Balved Education Foundation
SAE	Soxhlet-assisted extraction
SCE	sister chromatid exchange
SEM	scanning electron microscopy
SGPT	serum glutamate pyruvate transaminase
SGOT	serum glutamate oxaloacetate transferase
SOD	superoxide dismutase
SPF	sun protection factor
SuHV-1	suid herpesvirus type 1
STZ	streptozotocin
TB	T. *bellirica*
TBE	T. *bellirica* extract
TC	total cholesterol

TGs	triglycerides
TLC	thin layer chromatography
TNF	tumor necrosis factor
TST	tail suspension test
TT	thrombin time
Tb-01	isolated compound
UA	uric acid
VLDL	very low-density lipoprotein
WBC	white blood cells
XO	xanthine oxidase
5-HIAA	5-hydroxytryindole-3-acetic acid

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Preface

Many young researchers used to approach me with the question, "Can you suggest to me a medicinal plant on which I can work?" For answering this question, I had to dig into the literature on the bioactives and pharmacology. During this search, I found that comprehensive reviews on biomolecules and pharmacology for many medicinal plants are not available. With a view to fill this gap, we started this series of 10 volume books in the series AAP Focus on Medicinal Plants. This is the fourth book in this series. A comprehensive review on more than 80 plant species is given in this two-volume book.

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

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

I wish to express my gratitude to all the authors who contributed to the review chapters. I thank them for their cooperation and erudition.

I hope that this will be a source book for the development of new drugs. I request that readers give their suggestions to improve forthcoming volumes and future editions.

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CHAPTER 1

Ilex paraguariensis—Green Gold from South America

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ABSTRACT

Ilex paraguariensis A.St.-Hil. is a tree from South America known as yerba mate or maté with a natural occurrence in northwest Argentina, eastern Paraguay, and southern Brazil. It is the main non-timber forest product of these regions and has cultural and economic importance. Beyond these, its leaves and thin stalks have many bioactive compounds, especially chlorogenic acid isomers, caffeine, theobromine, rutin, and saponins. This bioactive-rich composition is related to some antiviral, antibacterial, antifungal, and antioxidant effects, as well as positive effects on blood glucose and dyslipidemia, neurological, and against a few tumor cells. Other emerging uses include natural food antioxidants, cosmetics, and active packaging. The *I.*

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paraguariensis extracts are very sensitive to heat, light, and oxygen, among other oxidizing conditions, and partial degradation during the gastrointestinal tract. The preservation strategies for the mate extract are challenging and promising.

1.1 INTRODUCTION

The botanical genus *Ilex* belongs to the Aquifoliaceae family, which is cosmopolitan and comprises about 500 species (Alikaridis, 1987). *Ilex paraguariensis* A.St.-Hil. is a native tree from South America known as yerba mate or maté and it has a natural distribution area of 540,000 km² between northwest Argentina, eastern Paraguay, and southern Brazil (Berté et al., 2011). In these regions, it has a great environmental and socioeconomic impact, as it is the main nontimber forest product, which increases local employment and income (Signor and Marcolini, 2017). Its leaves are traditionally consumed as a hot infusion (chimarrão), cold tea (tereré), or even as hot or cold roasted tea (mate tea). These products are usually made with the leaves and thin stalks (<10 mm) of the plant (Pagliosa et al., 2010).

Thus, there has been increasing interesting research and consumption of *I. paraguariensis* products, which are highly associated with scientific consolidation about the high concentration of beneficial bioactive compounds with functional properties. They include anti-inflammatory, antiobesogenic, antimutagenic, antibacterial, and antiviral capacity, as well as their antioxidant capacity, among others (Bisognin et al., 2019; Bracesco et al., 2011; De Mejía et al., 2010; Heck et al., 2008; Pagliosa et al., 2010). The *I. paraguariensis* compounds have been shown to have, besides health-promoting by consuming or from drugs and pharmaceuticals, also food fortification and preservation, and active packaging material (Azmir et al., 2013; Berté et al., 2011; Bracesco et al., 2011; Meinhart et al., 2017, 2018; Signor and Marcolini 2017).

1.2 BIOACTIVE COMPOUNDS

The extraction, concentration, and purification of bioactive compounds from *I. paraguariensis* have high technological and economic potential. The successful extraction of bioactive compounds from this plant material really upon several parameters, such as sampling, temperature, solvent type, and volume (water, ethanol, methanol, acetonitrile, acetone, or binary mixtures) (Azmir et al., 2013; Bastos et al., 2007a; Bisognin et al., 2019; Colpo et al.,

2016; Pilatti-Riccio et al., 2019; Pinto et al., 2021), and extraction procedures (solid–liquid partition; assisted extraction by ultrasound, microwave heating, pulsed electric field), and others (Azmir et al., 2013). The concentration of compounds and the guarantee of their stability are closely associated with postextraction processing, such as microfiltration and nanofiltration, cryo-concentration and encapsulation (Boaventura et al., 2013; Gerke et al., 2017; Murakami et al., 2013; Nunes et al., 2015; Pilatti-Riccio et al., 2019).

Other important parameters that influence the bioactive compounds from plant materials are related to the growing conditions and location (native-growing trees, agroforest systems, full sun exposure, soil fertility, and water), cultivars selection and breeding programs, as well as processing conditions and aging time (Bastos et al., 2007a; Croge et al., 2020; Dartora et al., 2011; Donaduzzi et al., 2003; Heck et al., 2008; Valduga et al., 2016; Zielinski et al., 2020). The processing also affects the composition of products derived from *I. paraguariensis*, as they include drying steps (using high temperatures), grinding, and granulometric standardization, among other specific steps for each product (Dartora et al., 2011; Heck et al., 2008; Isolabella et al., 2010; Nabechima et al., 2014; Obanda et al., 2001).

I. paraguariensis leaves and thin stalks have many bioactive compounds, especially phenolic acids such as the chlorogenic acid isomers (with a greater predominance of 3-caffeoylquinic acid, 4-caffeoylquinic acid, 5-caffeoylquinic acid, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, and 4,5-dicaffeoylquinic acid), also, quinic, caffeic, gallic, malic, p-coumaric, hydroxybenzoic, and ferulic acids. The phenolic acids stands high content about 10% in dry weight (Lorini et al., 2021; Meinhart et al., 2017, 2018).

In low concentration (between mg and ng/100 g of dry sample), other high biological interest compounds from leaves and stalks, which includes alkaloids, as cafeine and theobromine, flavonoids as quercetin, rutin, and kaempferol, carotenoids as lutein, condensed tannins, saponins, methylxanthines, chlorophylls, vitamins A, C, B1, B2, B6, some metals as iron, zinc, copper, manganese, calcium, sodium, potassium, aluminum, cadmium, chromium, strontium, magnesium, nickel, phosphorus and vanadium, as well as aspartic acid, glutamic acid, glycine, alanine, tryptophan, cystine, arginine, histidine, lysine, tyrosine, valine, leucine, isoleucine, threonine, methionine, asparagine, choline, nicotinic acid, pantothenic acid, ursolic acid, among others (Boaventura et al., 2015b; Bracesco, 2019; Bracesco et al., 2011; Isolabella et al., 2010; Lorini et al., 2021; Meinhart et al., 2018; Pagliosa et al., 2010; Pilatti-Riccio et al., 2019; da Silveira et al., 2016; Zielinski et al., 2020).

1.3 PHARMACOLOGY

1.3.1 ANTIVIRAL EFFECT

I. paraguariensis crude and purified extracts with monodesmosidic triterpenoid saponins, matesaponin-1 (a bidesmosidic one), caffeic and chlorogenic acids, and rutin have an antiviral effect against Herpes Simplex Virus (HSV) types 1 and 2 replication (Lückemeyer et al., 2012) and HSV-1 KOS and 29-R strains (Jang et al., 2008). 4,5 Dicaffeoylquinic acids is reported to inhibit the replication of HIV (Queffélec et al., 2008).

1.3.2 ANTIBACTERIAL ACTIVITY

The antibacterial activity of yerba mate extracts against Gram-positive bacteria such as *Staphylococcus aureus, Listeria monocytogenes* is often reported. However, antibacterial action against *Salmonella enteritidis*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* suggests that the activity of the extracts is not limited to Gram-positive bacteria, but extends to some Gram-negative species (Fayad et al., 2020; Kungel et al., 2018; Martin et al., 2013). Active compounds such as caffeine and chlorogenic acids have been highly associated with antibacterial activity in *S. aureus* when extracted with water, methanol, and ethanol (Fayad et al., 2020; Martin et al., 2013). However, ethanolic extracts are more effective than methanolic in inhibiting *S. aureus, L. monocytogenes*, and *S. enteritidis* (Martin et al., 2013). In addition, dialyzed extracts are efficient in reducing 4.5-log for *Escherichia coli* O157:H7 strains ATCC 43894 and "Cider" at pH 6 (Burris et al., 2012a, 2012b). Metabolites produced after in vitro digestion of *I. paragariensis* aqueous extracts gave similar antibacterial activity against *S. aureus* (Fayad et al., 2020).

1.3.3 ANTIFUNGAL ACTIVITY

The polysaccharide rhamnogalacturonan isolated from *I. paraguariensis* promotes the inhibition of *Aspergillus fumigatus*, *Aspergillus versicolor*, *Aspergillus ochraceus*, *Candida crusei*, *Penicillium funiculosum* and *Penicillium verrucosum* var. *ciclópico*, except for *Aspergillus niger* (Kungel et al., 2018). The topical uses of *I. paraguariensis* aqueous extract also have antifungal activity against *Malassezia furfur*, which causes pityriasis versicolor, dandruff, and seborrheic dermatitis in humans (Filip et al., 2010).

1.3.4 ANTIOXIDATIVE ACTIVITY

Several studies describe the antioxidant properties of *I. paraguariensis* extracts in the scavenging of free radicals, iron-chelating capacity, in preventing oxidative damage from lipids, and in increasing defense against oxidative stress (Boaventura et al., 2015b; Bracesco, 2019; Bracesco et al., 2011; Schinella et al., 2000). The main free radicals studied in vitro are DPPH and ABTS, and the scavenging of these radicals have a high correlation with the phenolic compounds from *I. paraguariensis* and its extracts (Boaventura et al., 2013; Hartwig et al., 2012; Pinto et al., 2021).

The phenolic compounds exhibit free radical scavenging and inhibit a chemically induced oxidation of lipid in membranes (Filip et al., 2000). The antioxidant activity and the concentration of bioactive compounds decrease after in vitro extracts' gastrointestinal digestion. However, digestion promotes considerable cellular antioxidant activity when compared to other undigested plant foods (Boaventura et al., 2015b).

Chronic inflammatory activity is a predisposing factor to comorbidities, the chronic noncommunicable diseases such as cancer, cardiovascular diseases, neurodegenerative diseases, obesity, and diabetes (Burris et al., 2012a, 2012b; Puangpraphant and De Mejia 2009). So, the ingestion of mate infusion (5 g of dried instant tea with 350 mg/g of total phenolics each day) for 7 days improve plasma susceptibility to oxidation and on antioxidant enzyme gene expression in healthy nonsmoking women, after acute or prolonged ingestion (De Morais et al., 2009).

The microencapsulated extract by ionic gelation was consumed for 30 days in male Wistar rats in vivo trial. The antioxidant activity reduced lipid peroxidation in the blood plasma and brain of animals, suggesting that microencapsulation enhances the bioactivity of *I. paraguariensis* extracts (Vargas et al., 2021).

The absorption and metabolism of phenolic compounds depend on a wide range of factors, including structure, bioaccessibility in relation to food matrix, gut microbiota, transporters, and metabolizing enzymes as well as the presence of other bioactive compounds (de Resende et al., 2015). The influence of these factors on the bioavailability of *I. paraguariensis* polyphenolics should also be considered (Cardozo Jr and Morand, 2016).

1.3.5 EFFECTS ON BLOOD GLUCOSE AND DYSLIPIDEMIA

Polyphenol-rich extracts from *I. paraguariensis* have been shown to inhibit the formation of advanced glycation end products (AGEs) or Maillard reaction products on a protein model in vitro, with an effect comparable to that

of two pharmaceutical-grade AGE inhibitor drugs (Lunceford and Gugliucci, 2005). The improvement in serum levels of glucose, creatinine, urea, and total protein is evident in diabetic rats after consumption of aqueous extract (Rocha et al., 2018).

The inhibition of low-density lipoprotein (LDL) oxidation is also widely described (Bastos et al., 2007b). In addition, the consumption of green or roasted infusions improves the serum lipid and provides an additional LDL-cholesterol reduction in individuals on statin therapy (De Morais et al., 2009). Mono- and di-caffeoylquinic acids also improve lipid metabolism and display antiobesity properties (Cho et al., 2010). It was demonstrated, through a meta-analysis, the positive effects of *I. paraguariensis* consumption on the reduction of body weight, body mass index, and waist circumference of patients, showing its antiobesity potential (Luís et al., 2019). However, special attention must be given due to the concentrations of each compound in the infusion or extracts to provide the desired benefits.

Antiobesity and antidiabetic effects were reported for *I. paraguariensis* in C57BL/6J mice fed a high-fat diet. The effects on lipid metabolism included reductions in serum cholesterol, serum triglycerides, and glucose in mice (Kang et al., 2012). Also, aqueous *I. paraguariensis* extracts reduce blood glucose, peripheral neuropathy, and oxidative damage in male mice exposed to streptozotocin, which may help to design therapeutic alternatives for the treatment of diabetes mellitus (de Lima et al., 2018).

The aqueous extract of *I. paraguariensis* is indicative of being a beneficial modulator of the metabolism of adipose tissue (WAT). It promotes a stock phenotype in both males and females and modulated lipogenic pathways in females (after ovariectomy or not), and lipolytic pathways in males Wistar rats (Rocha et al., 2021).

1.3.6 EFFECTS ON THE CARDIOVASCULAR SYSTEM

The daily intake of *I. paraguariensis* (1 g/kg body weight, in 1 mL water) for 7 days can protect the cardiac function against global ischemia/reperfusion damage, however, when associated low-intensity aerobic physical activity, the effect of both is attenuated (Cahuê et al., 2017).

1.3.7 NEUROLOGICAL EFFECTS

I. paraguariensis infusions (20 g of yerba/100 mL of distilled) provide neuroprotective effect against epilepsy pentylenetetrazol-induced seizures

(60 mg/kg of body weight) in Wistar rats, by having 50 mg/kg of infusion of body weight, for 15 days. The infusions also did not promote stimulant or depressive effects in the animals during the study (Branco et al., 2013).

1.3.8 EFFECTS AGAINST TUMOR CELLS

I. paraguariensis infusion has in vitro inhibition effect of colon cancer cell proliferation, preferentially inhibited 50% of net growth of human colorectal adenocarcinoma cells CaCo-2 (GI_{50} = 1.0 ± 0.03 µg/mL) and HT-29 (GI_{50} = 105.2 ± 15.2 µg/mL) when compared with the CCD-33Co normal colon fibroblast cell line (GI_{50} > 300 µg/mL). It also inhibited in vitro colon cancer cell proliferation possibly mediated via pro-oxidant activities, being a potential source of chemopreventive agent (de Mejía et al., 2010).

In vitro digested *I. paraguariensis* extracts inhibit the proliferation of $HepG_2$ human liver cancer cells (Boaventura et al., 2015a). Also, dicaffeoylquinic acids from yerba mate inhibit NF-κB nucleus translocation in macrophages and induce apoptosis by activating caspases-8 and -3 in human colon cancer cells (Lückemeyer et al., 2012).

1.4 OTHER EMERGING APPLICATIONS

Besides the vast pharmacological interest, a plant matrix in such evidence also stands out in the development of new hygiene and cleaning products, agricultural, food, packaging, cosmetics, dermatological, and others.

The aqueous and ethanolic extracts of *I. paraguariensis* have been used as antiseptic or disinfectant inputs, applicable in primary health care and production in small farming systems, with an emphasis on the prevention and control of *S. enteritidis* and *Enterococus faecalis* (Girolometto et al., 2009), serovars of *Salmonella* spp. of poultry origin (*Salmonella derby, Salmonella orion, Salmonella enteritidis, Salmonella enterica, Salmonella infantis, Salmonella mbandaka, Salmonella lexigton, Salmonella kentucky*) (De Bona et al., 2010).

The use of *I. paraguariensis* extracts promotes the inhibition of lipid oxidation in different foods. Thus, the inclusion of hydrogels formed by chia extract and oil resulted in a reduction in saturated fatty acids and an increase in omega-6 and omega-3 in buffalo meat hamburgers, and the extract inhibited the lipid oxidation of the products (Heck et al., 2021). Precooked chicken meatballs may accordingly be protected against lipid oxidation by

I. paraguariensis added before cooking (0.05% of dried leaves) either using the leaves or using an aqueous extract without affecting the flavor (Racanicci et al., 2008, 2009).

The dried leaves or extracts are efficient on the growth and zootechnical performance of different slaughter animals, underfeed supplementation. The dry extract of *I. paraguariensis* in the diet of growing lambs increase wool production, feed intake, levels of leukocyte cells, and globulins in the serum, while there was a reduction in LDL cholesterol and triglycerides (Lobo et al., 2020; Po et al., 2012). In addition, production and carcass yield has been improved, by the great production of lean tissue (Lobo et al., 2020). These behaviors are considered positive, as they lead to improvements in the health of consumers, generating healthier meat for the human diet and thus, more desired in the meat industry.

Packaging and cosmetic productions are the most promising emerging applications for *I. paraguariensis*. Starch biodegradable films are efficient in keeping the antioxidant properties (Knapp et al., 2019; Medina-Jaramillo et al., 2017) for food and nonfood application. Chitosan hydrochloride nanoparticles and microspheres incorporated by *I. paraguariensis* extract maintain antioxidant activity, have protective and hydrating characteristics, and have been identified as a potential way to incorporate natural antioxidants into cosmetics (Harris et al., 2011).

1.5 REMARKABLE TRENDS

One of the great challenges of science and technology is the fact that the bioactive compounds present in *I. paraguariensis* have low stability to heat, light, oxygen, among other oxidizing conditions. In addition, when the compounds are ingested, they undergo partial degradation during passage in the gastrointestinal tract (Gómez-Juaristi et al., 2018).

Therefore, preservation strategies for these compounds for late or controlled release have involved nanotechnological aspects, which include the formation of nanomaterials, including particles, capsules, fibers, gels, aerogels, hydrogels, liposomes, and others. In this context, the compounds of interest are involved and protected by wall materials or carriers, so that protection and release occur at a later time, in controlled or uncontrolled behavior.

The results are still scarce, but it has been observed that the encapsulation of extracts of *I. paraguariensis* results in the protection of compounds against oxidation, with increased antioxidant activity and increased bioavailability

in vivo (Córdoba et al., 2014; Dabulici et al., 2020; Fenoglio et al., 2021; Vargas et al., 2021), which shows the high potential of the use of nanotechnology and places it as a high scientific target. However, nanomaterials still deserving attention from regulatory affairs of the countries, and more and more research about their toxicological aspects.

KEYWORDS

- **maté**
- **phenolic compounds**
- **flavonoids**
- **antioxidative activity**
- **dyslipidemia control**

REFERENCES

Alikaridis, F. Natural Constituents of Ilex Species. *J. Ethnopharmacol.* **1987,** *20*, 121–144.

Azmir, J.; Zaidul, I. S. M.; Rahman, M. M.; Sharif, K. M.; Mohamed, A.; Sahena, F.; Jahurul, M. H. A.; Ghafoor, K.; Norulaini, N. A. N.; Omar, A. K. M. Techniques for Extraction of Bioactive Compounds from Plant Materials: A Review. *J. Food Eng.* **2013,** *117* (4), 426–436.

Bastos, D. H. M.; Saldanha, L. A.; Catharino, R. R.; Sawaya, A. C. H. F.; Cunha, I. B. S.; Carvalho, P. O.; Eberlin, M. N. Phenolic Antioxidants Identified by ESI-MS from Yerba Maté (*Ilex paraguariensis*) and Green Tea (*Camelia sinensis*) Extracts. *Molecules* **2007a,** *12* (3), 423–432.

Bastos, D. H. M.; de Oliveira, D. M.; Matsumoto, R. L. T.; Carvalho, P. O.; Ribeiro, M. L. Yerba Mate: Pharmacological Properties, Research and Biotechnology. *Med. Aromat. Plant Sci. Biotechnol.* **2007b,** *1* (1), 37–46.

Berté, K.; Rucker, N.; Hoffmann-Ribani, R. Yerba Maté *Ilex paraguariensis* A.St.-Hil. *Phytotherapie* **2011,** *9* (3), 180–184.

Bisognin, D. A.; da Luz, L. V.; Lencina, K. H.; dos Santos, C. O.; Sautter, C. K. Contents of Total Phenolics and Flavonoids in and Antioxidant Activity of *Ilex paraguariensis* Leaves. *Pesquisa Agropecuária Brasileira* **2019,** *54* (e00856), 1–8.

Boaventura, B. C. B.; Amboni, R. D. C.; da Silva, E. L.; Prudencio, E. S.; Di Pietro, P. F.; Malta, L. G.; Polinati, R. M.; Liu, R. H. Effect of in Vitro Digestion of Yerba Mate (*Ilex paraguariensis* A.St.Hil.) Extract on the Cellular Antioxidant Activity, Antiproliferative Activity and Cytotoxicity Toward HepG2 Cells. *Food Res. Int.* **2015a,** *77*, 257–263.

Boaventura, B. C. B.; Murakami, A. N. N.; Prudêncio, E. S.; Maraschin, M.; Murakami, F. S.; Amante, E. R.; Amboni, R. D. M. C. Enhancement of Bioactive Compounds Content and

Antioxidant Activity of Aqueous Extract of Mate (*Ilex paraguariensis* A.St.Hil.) Through Freeze Concentration Technology. *Food Res. Int.* **2013,** *53* (2), 686–692.

Boaventura, B. C. B.; da Silva, E. L.; Liu, R. H.; Prudêncio, E. S.; Di Pietro, P. F.; Becker, A. M.; Amboni, R. D. M. C. Effect of Yerba Mate (*Ilex paraguariensis* A.St.Hil.) Infusion Obtained by Freeze Concentration Technology on Antioxidant Status of Healthy Individuals. *LWT Food Sci. Technol.* **2015b,** *62* (2), 948–954.

Bracesco, N. *Ilex paraguariensis* as a Healthy Food Supplement for the Future World. *Biomed. J. Sci. Tech. Res.* **2019,** *16* (1), 11821–11823.

Bracesco, N.; Sanchez, A. G.; Contreras, V.; Menini, T.; Gugliucci, A. Recent Advances on *Ilex paraguariensis* Research: Mini Review. *J. Ethnopharmacol.* **2011,** *136* (3), 378–384.

Branco, C. S.; Scola, G.; Rodrigues, A. D.; Cesio, V.; Laprovitera, M.; Heinzen, H.; dos Santos, M. T.; Fank, B.; de Freitas, S. C. V.; Coitinho, A. S.; Salvador, M. Anticonvulsant, Neuroprotective and Behavioral Effects of Organic and Conventional Yerba Mate (*Ilex paraguariensis* St.Hil.) on Pentylenetetrazol-Induced Seizures in Wistar Rats. *Brain Res. Bull.* **2013,** *92*, 60–68.

Burris, K. P.; Davidson, P. M.; Stewart, C. N.; Zivanovic, S.; Harte, F. M. Aqueous Extracts of Yerba Mate (*Ilex paraguariensis*) as a Natural Antimicrobial Against *Escherichia coli* O157:H7 in a Microbiological Medium and pH 6.0 Apple Juice. *J. Food Prot.* **2012a,** *75* (4), 753–757.

Burris, K. P.; Harte, F. M.; Davidson, P. M.; Stewart Jr, C. N.; Zivanovic, S. 2012. Composition and Bioactive Properties of Yerba Mate (*Ilex paraguariensis* A.St.-Hil.): A Review. *Chil. J. Agric. Res.* **2012b,** *72* (2), 268–275.

Cahuê, F.; Souza, S.; dos Santos, C. F. M.; Machado, V.; Nascimento, J. H. M.; Barcellos, L.; Salermo, V. P. Short-Term Consumption of *Ilex paraguariensis* Extracts Protects Isolated Hearts from Ischemia/Reperfusion Injury and Contradicts Exercise-Mediated Cardioprotection. *Appl. Physiol. Nutr. Metab.* **2017,** *42* (11), 1–41.

Cardozo Jr., E. L.; Morand, C. Interest of Mate (*Ilex paraguariensis* A.St.-Hil.) as a New Natural Functional Food to Preserve Human Cardiovascular Health—A Review. *J. Funct. Foods* **2016,** *21*, 440–454.

Cho, A. S.; Jeon, S. M.; Kim, M. J.; Yeo, J.; Seo, K. I.; Choi, M. S.; Lee, M. K. Chlorogenic Acid Exhibits Anti-Obesity Property and Improves Lipid Metabolism in High-Fat Diet-Induced-Obese Mice. *Food Chem. Toxicol.* **2010,** *48* (3), 937–943.

Colpo, A. C.; Rosa, H.; Eduarda, M.; Eliza, C.; Pazzini, F.; De Camargo, V. B.; Bassante, F. E. M.; Puntel, R.; Silva, D.; Mendez, A.; Folmer, V. Yerba Mate (*Ilex paraguariensis* St. Hill.)-Based Beverages: How Successive Extraction Influences the Extract Composition and Its Capacity to Chelate Iron and Scavenge Free Radicals. *Food Chem.* **2016,** *209*, 185–95.

Córdoba, A. L.; Deladino, L.; Martino, M. Release of Yerba Mate Antioxidants from Corn Starch-Alginate Capsules as Affected by Structure. *Carbohydr. Polym.* **2014,** *99*, 150–157.

Croge, C. P.; Cuquel, F. L.; Pintro, P. T. M. Yerba Mate: Cultivation Systems, Processing and Chemical Composition: A Review. *Sci. Agricola* **2020,** *78* (5), 1–11.

Dabulici, C. M.; Sârbu, I.; Vamanu, E. The Bioactive Potential of Functional Products and Bioavailability of Phenolic Compounds. *Foods* **2020,** *9* (7), 953.

Dartora, N.; De Souza, L. M.; Santana-filho, A. P.; Iacomini, M.; Valduga, A. T.; Gorin, P. A. J.; Sassaki, G. L. UPLC-PDA—MS Evaluation of Bioactive Compounds from Leaves of *Ilex paraguariensis* with Different Growth Conditions, Treatments and Ageing. *Food Chem.* **2011,** *129* (4), 1453–1461.

da Silveira, T. F. F.; Meinhart, A. D.; Coutinho, J. P.; de Souza, T. C. L.; Cunha, E. C. E.; de Moraes, M. R.; Godoy, H. T. Content of Lutein in Aqueous Extracts of Yerba Mate (*Ilex paraguariensis* St. Hil). *Food Res. Int.* **2016,** *82*, 165–171.

De Bona, E. A. M.; Pinto, F. G. S.; Borges, A. C. M.; Weber, L. D.; Fruet, T. K.; Alves, L. F. A.; Moura, A. C. Avaliação Da Atividade Antimicrobiana de Erva-Mate (*Ilex paraguariensis*) Sobre Sorovares de *Salmonella* spp. de Origem Avícola. *Rev. Unopar Cient.* **2010,** *12* (3), 45–48.

de Lima, M. E.; Colpo, A. Z. C.; Rosa, H.; Salgueiro, A. C. F.; da Silva, M. P.; Noronha, D. S.; Santamaría, A.; Folmer, V. *Ilex paraguariensis* Extracts Reduce Blood Glucose, Peripheral Neuropathy and Oxidative Damage in Male Mice Exposed to Streptozotocin. *J. Funct. Foods* **2018,** *44*, 9–16.

de Mejía, E. G.; Song, Y. S.; Heck, C. I.; Ramírez-Mares, M. V. Yerba Mate Tea (*Ilex paraguariensis*): Phenolics, Antioxidant Capacity and In Vitro Inhibition of Colon Cancer Cell Proliferation. *J. Funct. Foods* **2010,** *2* (1), 23–34.

De Morais, E. C.; Stefanuto, A.; Klein, G. A.; Boaventura, B. C. B.; De Andrade, F.; Wazlawik, E.; Di Pietro, P. F.; Maraschino, M.; Da Silva, E. L. Consumption of Yerba Mate (*Ilex paraguariensis*) Improves Serum Lipid Parameters in Healthy Dyslipidemic Subjects and Provides an Additional LDL-Cholesterol Reduction in Individuals on Statin Therapy. *J. Agric. Food Chem.* **2009,** *57* (18), 8316–8324.

de Resende, P. E.; Kaiser, S.; Pittol, V.; Hoefel, A. L.; Silva, R. D.; Marques, C. V.; Kucharski, L. C.; Ortega G. G. Influence of Crude Extract and Bioactive Fractions of *Ilex praguariensis* A.St.Hil. (Yerba Mate) on the Wistar Rat Lipid Metabolism. *J. Funct. Foods* **2015,** *15*, 440–451.

Donaduzzi, C. M.; Cardozo Jr., E. L.; Donaduzzi, E. M.; da Silva, M. M.; Sturion, J. A.; Correa, G. Variação nos teores de polifenís totais e taninos em dezesseis progênies de Erva-Mate (*Ilex paraguariensis* St. Hill.) cultivadas em três municípios do Paraná. *Arquivos de Ciências Da Saúde Da Unipar* **2003,** *2* (7), 129–133.

Fayad, E.; El-Sawalhi, S.; Azizi, L.; Beyrouthy, M.; Abdel-Massih, R. M. Yerba Mate (*Ilex paraguariensis*) a Potential Food Antibacterial Agent and Combination Assays with Different Classes of Antibiotics. *LWT Food Sci. Technol.* **2020,** *125*, 109267.

Fenoglio, D.; Madrid, D. S.; Moyano, J. A.; Ferrario, M.; Guerrero, S.; Matiacevich, S. Active Food Additive Based on Encapsulated Yerba Mate (*Ilex paraguariensis*) Extract: Effect of Drying Methods on the Oxidative Stability of a Real Food Matrix (Mayonnaise). *J. Food Sci. Technol.* **2021,** *58* (4), 1574–1584.

Filip, R.; Davicino, R.; Anesini, C. Antifungal Activity of the Aqueous Extract of *Ilex paraguariensis* Against Malassezia Furfur. *Phytother. Res.* **2010,** 24, 715–719.

Filip, R.; Lotito, S. B.; Ferraro, G.; Fraga, C. G. Antioxidant Activity of *Ilex paraguariensis* and Related Species. *Nutr. Res.* **2000,** *20* (10), 1437–1446.

Gerke, I. B. B.; Hamerski, F.; Scheer, A. P.; Silva, V. R. Clarification of Crude Extract of Yerba Mate (*Ilex paraguariensis*) by Membrane Processes: Analysis of Fouling and Loss of Bioactive Compounds. *Food Bioprod. Process.* **2017,** *102*, 204–212.

Girolometto, G.; Avancini, C. A. M.; Carvalho, H. H. C.; Wiest, J. M. Antibacterial Activity of Yerba Mate (*Ilex paraguariensis* A.St.-Hil.) Extracts. *Rev. Bras. Plantas Med.* **2009,** *11* (1), 49–55.

Gómez-Juaristi, M.; Martínez-López, S.; Sarria, B.; Bravo, L.; Mateos, R. Absorption and Metabolism of Yerba Mate Phenolic Compounds in Humans. *Food Chem.* **2018,** *240*, 1028–1038.

Harris, R.; Lecumberri, E.; Mateos-Aparicio, I.; Mengíbar, M.; Heras, A. Chitosan Nanoparticles and Microspheres for the Encapsulation of Natural Antioxidants Extracted from *Ilex paraguariensis*. *Carbohydr. Polym.* **2011,** *84* (2), 803–836.

Hartwig, V. G.; Brumovsky, L. A.; Fretes, R. M.; Boado, L. S. 2012. Procedimento padronizado para avaliar a capacidade antioxidante dos extratos de Erva-Mate. *Ciencia e Tecnologia de Alimentos* **2012,** *32* (1), 126–133.

Heck, C. I.; Schmalko, M.; De Mejia, E. G. Effect of Growing and Drying Conditions on the Phenolic Composition of Mate Teas (*Ilex paraguariensis*). *J. Agric. Food Chem.* **2008,** *56* (18), 8394–8403.

Heck, R. T.; da Rosa, J. L.; Vendrusculo, R. G.; Cichoski, A. J.; Meinhart, A. D.; Lorini, A.; Paim, B. T.; Galli, V.; Robalo, S. S.; dos Santos, B. A.; de Pellegrin, L. F. V.; de Menezes, C. R.; Wagner, R.; Campagnol, P. C. B. Lipid Oxidation and Sensory Characterization of Omega-3 Rich Buffalo Burgers Enriched with Chlorogenic Acids from the Mate (*Ilex paraguariensis*) Tree harvesting Residues. *Meat Sci.* **2021,** *179*, 108534.

Isolabella, S.; Cogoi, L.; López, P.; Anesini, C.; Ferraro, G.; Filip, R. Study of the Bioactive Compounds Variation During Yerba Mate (*Ilex paraguariensis*) Processing. *Food Chem.* **2010,** *122* (3), 695–699.

Jang, M. H.; Piao, X. L.; Kim, J. M.; Kwon, S. W.; Park, J. H. Inhibition of Cholinesterase and Amyloid-&bgr; Aggregation by Resveratrol Oligomers from *Vitis amurensis*. *Phytother. Res.* **2008,** *22* (4), 544–549.

Kang, Y.-R.; Lee, H.-Y.; Kim, J.-H.; Moon, D.-I.; Seo, M.-Y; Park, S.-H.; Choi, K.-H.; Kim, C. R.; Kim, S.-H.; Oh, J.-H.; Cho, S.-W.; Kim, S.-Y.; Kim, M. G.; Chae, S. W.; Kim, O.; Oh, H.-G. Anti-Obesity and Anti-Diabetic Effects of Yerba Mate (*Ilex paraguariensis*) in C57BL/6J Mice Fed a High-Fat Diet. *Lab. Anim. Res.* **2012,** *28* (1), 23.

Knapp, M. A.; dos Santos, D. F.; Pilatti-Riccio, D.; Deon, V. G.; dos Santos, G. H. F.; Pinto, V. Z. Yerba Mate Extract in Active Starch Films: Mechanical and Antioxidant Properties. *J. Food Process. Preserv.* **2019,** *43* (3), 1–12.

Kungel, P. T. A. N.; Correa, V. G.; Corrêa, R. C. G.; Peralta, R. M. R. A.; Calhelha, M. S. R. C.; Bracht, A.; Ferreira, I. C. F. R.; Peralta, R. M. R. A. Antioxidant and Antimicrobial Activities of a Purified Polysaccharide from Yerba Mate (*Ilex paraguariensis*). *Int. J. Biol. Macromol.* **2018,** *114*, 1161–1167.

Lobo, R. R. R.; Vincenzi, R.; Rojas-Moreno, D. A. A.; Lobo, A. A. G. A. G.; da Silva, C. M. M.; Benetel-Junior, V.; Ghussn, L. R. R.; Mufalo, V. C. C.; Berndt, A.; Gallo, S. B. B..; Pinheiro, R. S. B. S. B.; Bueno, I. C. d. S. C. d. S.; Faciola A. P. P. Inclusion of Yerba Mate (*Ilex paraguariensis*) Extract in the Diet of Growing Lambs: Effects on Blood Parameters, Animal Performance, and Carcass Traits. *Animals* **2020,** *10* (6), 1–14.

Lorini, A.; Damin, F. M.; de Oliveira, D. N.; Crizel, R. L.; Godoy, H. T.; Galli, V.; Meinhart, A. D. Characterization and Quantification of Bioactive Compounds from *Ilex paraguariensis* Residue by HPLC-ESI-QTOF-MS from Plants Cultivated Under Different Cultivation Systems. *J. Food Sci.* **2021,** *86* (5), 1599–1619.

Lückemeyer, D. D.; Müller, V. D. M.; Moritz, M. I. G.; Stoco, P. H.; Schenkel, E. P.; Barardi, C. R. M.; Reginatto, F. H.; Simões, C. M. O. Effects of *Ilex paraguariensis* A.St.Hil. (Yerba Mate) on Herpes Simplex Virus Types 1 and 2 Replication. *Phytother. Res.* **2012,** *26* (4), 535–540.

Luís, A. F. S.; Domingues, F. d. C.; Amaral, L. M. J. P. The Anti-Obesity Potential of *Ilex paraguariensis*: Results from a Meta-Analysis. *Braz. J. Pharm. Sci.* **2019,** *55* (e17615), 1–15.

Lunceford, N.; Gugliucci, A. *Ilex paraguariensis* Extracts Inhibit AGE Formation More Efficiently than Green Tea. *Fitoterapia* **2005,** 76 (5), 419–427.

Martin, J. G. P.; Porto, E.; De Alencar, S. M.; Glória, E. M.; Corrêa, C. B.; Cabral, I. S. R. Antimicrobial Activity of Yerba Mate (*Ilex paraguariensis* St.Hil.) Against Food Pathogens. *Rev. Argent. Microl.* **2013,** *45* (2), 93–98.

Medina-Jaramillo, C.; Ochoa-Yepes, O.; Bernal, C.; Famá L. Active and Smart Biodegradable Packaging Based on Starch and Natural Extracts. *Carbohydr. Polym.* **2017,** *176*, 187–194.

Meinhart, A. D.; Lucas, C.; Damin, F. M.; Filho, J. T.; Godoy, H. T. Analysis of Chlorogenic Acids Isomers and Caffeic Acid in 89 Herbal Infusions (Tea). *J. Food Compos. Anal.* **2018,** *73*, 76–82.

Meinhart, A. D.; Damin, F. M.; Caldeirão, L.; da Silveira, T. F. F.; Filho, J. T.; Godoy, H. T. Chlorogenic Acid Isomer Contents in 100 Plants Commercialized in Brazil. *Food Res. Int.* **2017,** *99*, 522–530.

Murakami, A. N. N.; Amboni, R. D. d. M. C.; Prudêncio, E. S.; Amante, E. R.; Fritzen-Freire, C. B.; Boaventura, B. C. B.; Muñoz, I. D. B.; Branco, C. D. S.; Salvador, M.; Maraschin M. Concentration of Biologically Active Compounds Extracted from *Ilex paraguariensis* St.Hil. by Nanofiltration. *Food Chem.* **2013,** *141* (1), 60–65.

Nabechima, G. H.; Provesi, J. G.; Frescura, J. D. O.; Mantelli, M. B. H.; Vieira, M. A.; Prudêncio, E. S.; Amante, E. R. Thermal Inactivation of Peroxidase and Polyphenoloxidase Enzymes in Mate Leaves (*Ilex paraguariensis*) in a Conveyor Belt Oven. *CYTA J. Food* **2014,** *12* (4), 399–406.

Nunes, G. L.; Boaventura, B. C. B.; Pinto, S. S.; Verruck, S.; Murakami, F. S.; Prudêncio, E. S.; Amboni, R. D. D. M. C. Microencapsulation of Freeze Concentrated *Ilex paraguariensis* Extract by Spray Drying. *J. Food Eng.* **2015,** *151*, 60–68.

Obanda, M. P.; Okinda, O.; Mang'oka, R. Changes in the Chemical and Sensory Quality Parameters of Black Tea Due to Variations of Fermentation Time and Temperature. *Food Chem.* **2001,** *75* (4), 395–404.

Pagliosa, C. M.; Vieira, M. A.; Podestá, R.; Maraschin, M.; Zeni, A. L. B.; Amante, E. R.; Castanho Amboni R. D. d. M. C. Methylxanthines, Phenolic Composition, and Antioxidant Activity of Bark from Residues from Mate Tree Harvesting (*Ilex paraguariensis* A.St.Hil.). *Food Chem.* **2010,** *122* (1), 173–178.

Pilatti-Riccio, D.; dos Santos, D. F.; Meinhart, A. D.; Knapp, M. A.; Hackbart, H. C. D. S.; Pinto, V. Z. Impact of the Use of Saccharides in the Encapsulation of *Ilex paraguariensis* Extract. *Food Res. Int.* **2019,** *125*, 108600.

Pinto, V. Z.; Pilatti-Riccio, D.; da Costa, E. S.; Micheetto, Y. M. S.; Quast, E.; dos Santos, G. H. F. Phytochemical Composition of Extracts from Yerba Mate Chimarrão. *SN Appl. Sci.* **2021,** *3*, 1–5.

Po, E.; Horsburgh, K.; Raadsma, H. W.; Celi, P. Yerba Mate (*Ilex paraguarensis*) as a Novel Feed Supplement for Growing Lambs. *Small Rumin. Res.* **2012,** *106* (2–3), 131–36.

Puangpraphant, S.; De Mejia, E. G. Saponins in Yerba Mate Tea (*Ilex paraguariensis* A. St.-Hil) and Quercetin Synergistically Inhibit INOS and COX-2 in Lipopolysaccharide-Induced Macrophages Through NFκB Pathways. *J. Agric. Food Chem.* **2009,** *57* (19), 8873–8883.

Queffélec, C.; Bailly, F.; Mbemba, G.; Mouscadet, J. F.; Hayes, S.; Debyser, Z.; Witvrouw, M.; Cotelle, P. Synthesis and Antiviral Properties of Some Polyphenols Related to *Salvia* Genus. *Bioorg. Med. Chem. Lett.* **2008,** *18* (16), 4736–4740.

Racanicci, A. M. C.; Danielsen, B.; Skibsted, L. H. Mate (*Ilex paraguariensis*) as a Source of Water Extractable Antioxidant for Use in Chicken Meat. *Eur. Food Res. Technol.* **2008,** *227* (1), 255–260.

Racanicci, A. M. C.; Helene, B.; Skibsted, L. H. Sensory Evaluation of Precooked Chicken Meat with Mate (*Ilex paraguariensis*) Added as Antioxidant. *Eur. Food Res. Technol.* **2009,** *229*, 277–280.

Rocha, D. S.; Model, J. F. A.; Von Dentz, M.; Maschio, J.; Ohlweiler, R.; Lima, M. V.; de Souza, S. K.; Sarapio, E.; Vogt, É. L.; Waszczuk, M.; Martiny, S.; Bassani, V. L.; Kucharski, L. C. Adipose Tissue of Female Wistar Rats Respond to *Ilex paraguariensis* Treatment After Ovariectomy Surgery. *J. Trad. Complement. Med.* **2021,** *11* (3), 238–248.

Rocha, D. S.; Casagrande, L.; Model, J. F. A.; dos Santos, J. T.; Hoefel, A. L.; Kucharski, L. C. Effect of Yerba Mate (*Ilex paraguariensis*) Extract on the Metabolism of Diabetic Rats. *Biomed. Pharmacother.* **2018,** *105*, 370–376.

Schinella, G. R.; Troiani, G.; Daávila, V.; De Buschiazzo, P. M.; Tournier, H. A. Antioxidant Effects of an Aqueous Extract of *Ilex paraguariensis*. *Biochem. Biophys. Res. Commun.* **2000,** *269* (2), 357–360.

Signor, P.; Marcolini, M. *Diagnóstico Do Consumo Industrial de Erva-Mate No Paraná*; Instituto de Florestas Do Paraná, 2017.

Valduga, A. T.; Dartora, N.; Mielniczki-pereira, A. A.; De Souza, L. M. Phytochemical Profile of Morphologically Selected Yerba-Mate Progenies. **2016,** *40* (1), 114–120.

Vargas, B. K.; Frota, E. G.; dos Santos, L. F.; Gutkoski, J. P.; Lopes, S. T.; Bertol, C. D.; Bertolin, T. E. Yerba Mate (*Ilex paraguariensis*) Microparticles Modulate Antioxidant Markers in the Plasma and Brains of Rats. *Food Biosci.* **2021,** *41*, 100999.

Zielinski, A. A. F.; Alberti, A.; Bona, E.; Bortolini, D. G.; Benvenutti, L.; Bach, F.; Demiate, I. M.; Nogueira, A. A Multivariate Approach to Differentiate Yerba Mate (*Ilex paraguariensis*) Commercialized in the Southern Brazil on the Basis of Phenolics, Methylxanthines and In Vitro Antioxidant Activity. *Food Sci. Technol.* **2020,** *40* (3), 645–652.

CHAPTER 2

The Pharmacological Properties of Brazilian Arnica (*Solidago chilensis* Meyen)

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ABSTRACT

Solidago chilensis Meyen is a medicinal plant native from South America, popularly known in Brazil as "arnica". This species is used in folk medicine to treat several diseases such as wound healing, muscle pain and inflammatory diseases. These properties can be associated with the presence of bioactive compounds such as caffeoylquinic acids, flavonoids, and terpenes. Indeed, extracts of different parts of this plant showed anti-inflammatory effects in both in vitro and vivo approaches. Moreover, preclinical studies demonstrated the action of *S. chilensis* extracts and isolated compounds in nociception, production of reactive oxygen species, gastroprotection, lipid and glucose metabolism, and proliferation of cancer cells, thus, corroborating the popular use of the plant.

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2.1 INTRODUCTION

Solidago chilensis Meyen, popularly known in Brazil as "arnica," "arnica-brasileira," "arnica-silvestre," "lancet," "erva-lanceta," "espiga-ouro," and "rabo-de-foguete" figures in the National List of Medicinal Plants of Interest to SUS (Brazilian National Public Health System; RENISUS). This plant of the Asteraceae family is native to South America and is present in Northeast, Midwest, Southeast, and South Brazilian regions (Borges and Teles, 2015). It is a subshrub measuring 80–120 cm in height, composed of abundant rhizomes and erect stem, with inflorescences of yellow/golden color, pyramidal or spearhead-shaped at its apical end (Brito et al., 2020; Valverde et al., 2020). Its main synonyms are *Solidago linearifolia* DC. and *Solidago microglossa* DC.

This species is widely used in folk medicine in the form of maceration, teas, and infusions of leaves, stems, rhizomes, and inflorescences for diverse diseases such as wound healing, muscle pain, inflammatory diseases, respiratory diseases, bruises, bone fractures, gastrointestinal diseases, and rheumatic diseases (Bieski et al., 2015; Tuler and da Silva, 2014; Goleniowski et al., 2006; Magalhães et al., 2019; Ribeiro et al., 2017; Tribess et al., 2015).

2.2 BIOACTIVES

The main components found in the hydroalcoholic extract of aerial parts of *S. chilensis* were caffeoylquinic acids and flavonoids such as rutin, quercetin, and quercitrin (Tamura et al., 2009; Vechia et al., 2016). In the ethanolic extract obtained from the inflorescences were identified the compounds quinic acid, quercetin, chlorogenic acid, hyperoside, and rutin (Vogas et al., 2020). Also, flavonoids derived from quercetin and kaempferol were identified in the ether–ethanol extract obtained from inflorescences (Brito et al., 2020). Terpenes were also identified in this species. The solidagenone is a diterpene abundant in the rhizomes (Schmeda-Hirschmann, 1988). The pumiloxide, a labdane diterpene, was found as the major component of the volatile substances of essential oil (EO) from leaves and inflorescences (Vila et al., 2002). Germacrene D and limolene are the major components in the volatile compounds of the stem, fresh and dry inflorescences (Valverde et al., 2020).

2.3 PHARMACOLOGY

2.3.1 ANTI-INFLAMMATORY

One of the main uses of *S. chilensis* aqueous extract (AE) is to treat inflammatory disorders. This effect was investigated using in vivo and in vitro preclinical studies. Treatment with the ether–ethanol extract obtained from the inflorescences was able to inhibit the production of nitric oxide (NO) induced by lipopolysaccharide (LPS) in a murine macrophage cell line J774A.1 (Brito et al., 2020). Another in vitro study with the HeLa cell line showed that treatment with this extract exerts an effect on the transcriptional activity of peroxisome proliferator-activated receptor-gamma, a nuclear receptor linked to the anti-inflammatory response (Vogas et al., 2020).

The AE of aerial parts, inflorescences, and rhizomes inhibited leukocyte migration and exudation in a carrageenan-induced pleurisy model (Goulart et al., 2007). Neutrophils were the main leukocytes with inhibited migration and this effect was related to decreased levels of myeloperoxidase (MPO), NO, and the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-β (IL-1β) (Goulart et al., 2007; Liz et al., 2008).

The anti-inflammatory effects of this plant were also demonstrated for the hydroalcoholic extract in an ear inflammation model, in which the topical treatment had a stronger effect than the intraperitoneal route. Moreover, the oral treatment was not able to reduce edema in the ear region, suggesting a poor bioavailability of anti-inflammatory components due to first-pass metabolism or degradation due to the pH of the stomach or intestine (Tamura et al., 2009). This study also observed that the intraperitoneal treatment reduced the migration of polymorphonuclear leukocytes to the site of inflammation, which may explain the reduction in ear edema.

Solidagenone diterpene isolated from the rhizomes of *S. chilensis* inhibited the inflammatory process in several models of ear edema in mice, by decreasing vasodilation, local edema, and leukocyte migration (Valverde et al., 2021). This study also showed that this diterpene interfered with the signaling pathways of inflammatory factors such as cyclooxygenase-1 and prostaglandin E2 9-reductase inhibitors.

2.3.2 ANTINOCICEPTIVE EFFECT

The hydroalcoholic extract of aerial parts of the *S. chilensis* showed antinociceptive activity in animal models such as sensitivity to heat and mechanical

stimuli, probably by a specific noninflammatory antinociceptive mechanism (Malpezzi-Marinho et al., 2019). The effect on nociception was also verified in the acetic acid-induced writhing test and formalin test in mice. The AE administered orally to mice was able to reduce the licking time in both phases of the formalin test, suggesting an antinociceptive and anti-inflammatory effect (Assini et al., 2013). The volatile fraction of EO extracted from fresh and dry inflorescences were able to reduce around 50% of the writhing in animals; this effect was attributed to limonene and germacrene D compounds present in the fraction (Valverde et al., 2020).

In a preliminary clinical study, a decrease in the perception of pain in the hand and wrists was observed in individuals who received an application of the gel containing an alcoholic extract of *S. chilensis* compared with the placebo group, probably due to an anti-inflammatory action (da Silva et al., 2015). Also, the glycolic extract had a similar effect in the treatment of lumbago, with decreased pain perception in the lumbar region and increased flexibility when compared to the placebo group (da Silva et al., 2010).

2.3.3 ANTIOXIDANT EFFECT

The ethanol extract and fractions of *S. chilensis* had a greater antioxidant activity compared with the antioxidant BHT, that may be due to the presence of flavonoids, which are capable of interrupting radical reactions (Güntner et al., 1999). A tincture with this plant also presented an antioxidant activity through the quantitative 2,2-diphenyl-1-picryl-hydrazyl-hydrate assay (Gastaldi et al., 2016). The AE of the aerial parts of this plant is rich in flavonoids such as quercetin, which would justify the antioxidant effect of this extract (Gastaldi et al., 2018).

2.3.4 ANTIMICROBIAL ACTIVITY

The *S. chilensis* AE was active only against Gram-positive bacteria (Avancini et al., 2008), while, the AE and the butanolic fraction of the rhizome inhibited the growth of Gram-negative bacteria such as *Pseudomonas aeruginosa* with the minimum inhibitory concentration (MIC) value of 3.1 mg/mL (AE) and 12.5 mg/mL (butanolic fraction, BuOH) and *Escherichia coli* with a MIC of 6.2 mg/mL for both AE and BuOH (Liz et al., 2009). Also, the alcoholic extract was able to reduce the growth of *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter cloacae*, *Morganella morganii*, *Acinetobacter baumannii*, *P.*

aeruginosa, and *Stenotrophomonas maltophilia* (Zampini et al., 2007). The hydroalcoholic extract had strong antimicrobial activity against *Staphylococcus aureus* with a MIC of 0.1 mg/mL (Duarte et al., 2004).

The antifungal effect of EOs from leaves and inflorescences of *S. chilensi*s was demonstrated against the dermatophyte fungi *Microsporum gypseum* and *Trichophyton mentagrophytes*, but it was not capable to inhibit the growth of other filamentous fungi. Pumiloxide is likely the phytochemical responsible for this antifungal activity (Vila et al., 2002).

2.3.5 GASTROPROTECTIVE EFFECT

S. chilensis AE is used in folk medicine to treat gastrointestinal diseases (Bucciarelli and Skliar, 2007; Goleniowski et al., 2006). In a model of ethanol-induced ulcers in mice of the CF-1 strain, the AE of inflorescences had a gastroprotective effect at doses of 125, 250, and 400 mg/kg compared with the control (omeprazole), although it did not completely inhibit ulcer formation. In two animals, the formation of ulcers was not observed in the animals treated with the doses of 800, 1200, and 2000 mg/kg (Bucciarelli et al., 2010).

The methanol extract of this plant also reduced the area of ulcers induced by the administration of ethanol/chloride acid in mice. In addition, there was observed an increase in the levels of the glutathione, decreased activity of MPO and TNF-α levels compared with the control group. These protective effects were attributed to the flavonoids quercetin and afzelin, conferring antisecretory, antioxidant and anti-inflammatory properties (de Barros et al., 2016).

Solidagenone may also be responsible for the gastroprotective activity (Schmeda-Hirschmann et al., 2002). This diterpene was able to increase the defensive factors of the gastric mucosa of mice in three different models of gastric ulcer, probably independent of endogenous prostaglandins (Rodríguez et al., 2002).

2.3.6 ANTIDEPRESSIVE EFFECT

In a model of LPS-induced depression, solidagenone isolated from *S. chilensis* leaves was able to reduce depression in mice. This effect was related to the reduction of inflammatory processes, such as the decrease of IL-6 and TNF-α levels and the regulation of antioxidant mechanisms (Locateli et al., 2020).

2.3.7 HYPOLIPIDEMIC AND HYPOGLYCEMIC EFFECT

The hydroalcoholic extract of *S. chilensis* was tested in rats conditioned to a hyperlipidemic diet. The oral treatment with the compound and also with the isolated flavonoid quercetin diminished the lipid levels in the blood of the animals, possibly by reducing the activity of the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase and the antioxidant action (Roman et al., 2015). In addition to the hypolipidemic effect, the rodents submitted to the oral treatment with the extract had increased insulin production and secretion as well as augmented the insulinotropic activity, resulting in a reduction in the glucose levels in the bloodstream (Schneider et al., 2015).

2.3.8 PROLIFERATION, CELL VIABILITY, AND TOXIC EFFECTS

No signs of cytotoxicity were found after 24 h of incubation of L929 with the methanolic extract of *S. chilensis* (de Barros et al., 2016). In another study, Brito and colleagues (2020) observed the cytotoxicity of ether–ethanol extract from the inflorescence in J774A.1 cells. The concentrations of 100 and 200 μg/mL decreased macrophage viability by 71% and 100%, respectively, while other lower concentrations tested (1 and 10 ug/mL) were not toxic, keeping the viability of these cells above 90%.

The lyophilized AE of this plant had a great antiproliferative effect in T84 colon adenocarcinoma and HTR/SVneo trophoblast cell lines, with an inhibitory concentration (IC_{50}) of 0.16 ± 0.07 and 0.24 ± 0.03, respectively, with gallic acid being the main responsible for this antiproliferative effect (Gastaldi et al., 2018). Solidagenone, one of the main components of the dichloromethane extract from aerial parts of *S. chilensis*, also had in vitro antiproliferative effect on tumors cell lines of the breast (MCF-7), kidney (786-0), and prostate cancer (PC-3). These effects are possibly due to the interaction of this compound with nuclear receptors and as an enzyme inhibitor (Gomes et al., 2018).

Oral administration of the AE of *S. chilensis* did not produce histopathological, neuromotor, sensory, or autonomic system changes, thus demonstrating the absence of acute toxicity of this extract (Bucciarelli et al., 2010).

KEYWORDS

- **Asteraceae**
- **pharmacology**
- **inflammation**
- **folk medicine**
- **arnica-brasileira**

REFERENCES

Assini, F. L.; Fabrício, E. J.; Lang, K. L. Efeitos farmacológicos do extrato aquoso de *Solidago chilensis* Meyen em camundongos. *Revista Brasileira de Plantas Medicinais* **2013,** *15* (1), 130–134.

Avancini, C.; Wiest, J. M.; Dall'Agnol, R.; Haas, J. S.; von Poser, G. L. Antimicrobial Activity of Plants Used in the Prevention and Control of Bovine Mastitis in Southern Brazil. *Lat. Am. J. Pharm.* **2008,** *27* (6), 894–899.

de Barros, M.; Da Silva, L. M.; Boeing, T.; Somensi, L. B.; Cury, B. J.; de Moura Burci, L.; et al. Pharmacological Reports About Gastroprotective Effects of Methanolic Extract from Leaves of *Solidago chilensis* (Brazilian Arnica) and Its Components Quercitrin and Afzelin in Rodents. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2016,** *389* (4), 403–417.

Bieski, I. G. C.; Leonti, M.; Arnason, J. T.; Ferrier, J.; Rapinski, M.; Violante, I. M. P.; et al. Ethnobotanical Study of Medicinal Plants by Population of Valley of Juruena Region, Legal Amazon, Mato Grosso, Brazil. *J. Ethnopharmacol.* **2015,** *173*, 383–423.

Borges, R. A. X.; Teles, A. M. *Solidago chilensis* Meyen. Lista de Espécies Da Flora Do Brasil. Jardim Botânico Do Rio de Janeiro. 2015. http://floradobrasil.jbrj.gov.br/jabot/FichaPublicaTaxonUC/FichaPublicaTaxonUC.do?id=FB5503 (accessed on April 21, 2021).

Brito, T. M. D.; Amendoeira, F. C.; Oliveira, T. B. D.; Frutuoso, V. D. S.; Ferraris, F. K.; Valverde, S. S. Extract of *Solidago chilensis* Meyen Inflorescences: Cytotoxicity and Inhibitory Activity on Nitric Oxide Synthesis in Activated Macrophage Cell Line J774A. 1. *Braz. J. Pharm. Sci.* **2020,** *56*, e17707.

Bucciarelli, A.; Minetti, A.; Milczakowskyg, C.; Skliar, M. Evaluation of Gastroprotective Activity and Acute Toxicity of *Solidago chilensis* Meyen (Asteraceae). *Pharm. Biol.* **2010,** *48* (9), 1025–1030.

Bucciarelli, A. Y.; Skliar, M. I. Plantas medicinales de Argentina con actividad gastroprotectora. *Ars. Pharm.* **2007,** *48* (4), 361–369.

Duarte, M. C. T.; Figueira, G. M.; Pereira, B.; Magalhães, P. M.; Delarmelina, C. Atividade antimicrobiana de extratos hidroalcólicos de espécies da coleção de plantas medicinais CPQBA/UNICAMP. *Revista Brasileira de Farmacognosia* **2004,** *14*, 6–8.

Gastaldi, B.; Assef, Y.; van Baren, C.; Lira, P. D. L.; Retta, D.; Bandoni, A. L.; González, S. B. Antioxidant Activity in Teas, Tinctures and Essential Oils of Native Species from Patagonia Argentina. *Rev. Cubana Plantas Med.* **2016,** *21* (1), 51–62.

Gastaldi, B.; Marino, G.; Assef, Y.; Sofrás, F. S.; Catalán, C. A. N.; González, S. B. Nutraceutical Properties of Herbal Infusions from Six Native Plants of Argentine Patagonia. *Plant Foods Hum. Nutr.* **2018,** *73* (3), 180–188.

Goleniowski, M. E.; Bongiovanni, G. A.; Palacio, L.; Nuñez, C. O.; Cantero, J. J. Medicinal Plants from the "Sierra de Comechingones", Argentina. *J. Ethnopharmacol.* **2006,** *107* (3), 324–341.

Gomes, D. B.; Zanchet, B.; Locateli, G.; Benvenutti, R. C.; Dalla Vechia, C. A.; Schönell, A. P.; et al. Antiproliferative Potential of Solidagenone Isolated of *Solidago chilensis. Rev. Bras. Farmacogn.* **2018,** *28* (6), 703–709.

Goulart, S.; Moritz, M. I. G.; Lang, K. L.; Liz, R.; Schenkel, E. P.; Fröde, T. S. Anti-Inflammatory Evaluation of *Solidago chilensis* Meyen in a Murine Model of Pleurisy. *J. Ethnopharmacol.* **2007,** *113* (2), 346–353.

Güntner, C.; Barra, C.; Cesio, M. V.; Dellacassa, E.; Ferrando, L.; Ferreira, F.; García, C.; González, G.; Heinzen, H.; Lloret, A.; Lorenzo, D.; Menéndez, P.; Paz, D.; Soule, S.; Vázquez, A.; Moyna, P. Antioxidant Properties of *Solidago chilensis* l. Flavonoids. *Acta Hortic*. **1999,** *501*, 159–164.

Liz, R.; Neiva, T.; Moritz, M. I. G.; Dalmarco, E. M.; Fröde, T. S. Evaluation of Antimicrobial and Antiplatelet Aggregation Effects of *Solidago chilensis* Meyen. *Int. J. Green Pharm.* **2009,** *3* (1), 35–39.

Liz, R.; Vigil, S. V. G.; Goulart, S.; Moritz, M. I. G.; Schenkel, E. P.; Fröde, T. S. The Anti-Inflammatory Modulatory Role of *Solidago chilensis* Meyen in the Murine Model of the Air Pouch. *J. Pharm. Pharmacol.* **2008,** *60* (4), 515–521.

Locateli, G.; de Oliveira Alves, B.; Miorando, D.; Ernetti, J.; Alievi, K.; Zilli, G. A. L.; et al. Antidepressant-Like Effects of Solidagenone on Mice with Bacterial Lipopolysaccharide (LPS)-Induced Depression. *Behav. Brain Res.* **2020,** *395*, 112863.

Magalhães, K. do N.; Guarniz, W. A. S.; Sá, K. M.; Freire, A. B.; Monteiro, M. P.; Nojosa, R. T.; et al. Medicinal Plants of the Caatinga, Northeastern Brazil: Ethnopharmacopeia (1980–1990) of the Late Professor Francisco José de Abreu Matos. *J. Ethnopharmacol.* **2019,** *237*, 314–353.

Malpezzi-Marinho, E. L.; Molska, G. R.; Freire, L. I.; Silva, C. I.; Tamura, E. K.; Berro, L. F.; et al. Effects of Hydroalcoholic Extract of *Solidago chilensis* Meyen on Nociception and Hypernociception in Rodents. *BMC Complem. Atern. Med.* **2019,** *19* (1), 1–9.

Ribeiro, R. V.; Bieski, I. G. C.; Balogun, S. O.; de Oliveira Martins, D. T. Ethnobotanical Study of Medicinal Plants Used by Ribeirinhos in the North Araguaia Microregion, Mato Grosso, Brazil. *J. Ethnopharmacol.* **2017,** *205*, 69–102.

Rodríguez, J. A.; Bustamante, C.; Astudillo, L.; Schmeda-Hirschmann, G. Gastroprotective Activity of Solidagenone on Experimentally-Induced Gastric Lesions in Rats. *J. Pharm. Pharmacol.* **2002,** *54* (3), 399–404.

Roman Jr., W. A.; Piato, A. L.; Conterato, G. M.; Wildner, S. M.; Marcon, M.; Mocelin, R.; et al. Hypolipidemic Effects of *Solidago chilensis* Hydroalcoholic Extract and Its Major Isolated Constituent Quercetrin in Cholesterol-Fed Rats. *Pharm. Biol.* **2015,** *53* (10), 1488–1495.

Schmeda-Hirschmann, G. S. A Labdan Diterpene from *Solidago chilensis* Roots. *Planta Med.* **1988,** *54* (2), 179–180.

Schmeda-Hirschmann, G.; Rodriguez, J.; Astudillo, L. Gastroprotective Activity of the Diterpene Solidagenone and Its Derivatives on Experimentally Induced Gastric Lesions in Mice. *J. Ethnopharmacol.* **2002,** *81* (1), 111–115.

Schneider, M.; Sachett, A.; Schönell, A. P.; Ibagy, E.; Fantin, E.; Bevilaqua, F.; et al. Hypoglycemic and Hypolipidemic Effects of *Solidago chilensis* in Rats. *Rev. Bras. Farmacogn.* **2015,** *25* (3), 258–263.

da Silva, A. G.; de Sousa, C. P.; Koehler, J.; Fontana, J.; Christo, A. G.; Guedes-Bruni, R. R. Evaluation of an Extract of Brazilian Arnica (*Solidago chilensis* Meyen, Asteraceae) in Treating Lumbago. *Phytother. Res.* **2010,** *24* (2), 283–287.

da Silva, A. G.; Machado, E. R.; de Almeida, L. M.; Menezes Nunes, R. M.; Giesbrecht, P. C. P.; Costa, R. M.; et al. A Clinical Trial with Brazilian Arnica (*Solidago chilensis* Meyen) Glycolic Extract in the Treatment of Tendonitis of Flexor and Extensor Tendons of Wrist and Hand. *Phytother. Res.* **2015,** *29* (6), 864–869.

Tamura, E. K.; Jimenez, R. S.; Waismam, K.; Gobbo-Neto, L.; Lopes, N. P.; Malpezzi-Marinho, E. A.; et al. Inhibitory Effects of *Solidago chilensis* Meyen Hydroalcoholic Extract on Acute Inflammation. *J. Ethnopharmacol.* **2009,** *122* (3), 478–485.

Tribess, B.; Pintarelli, G. M.; Bini, L. A.; Camargo, A.; Funez, L. A.; de Gasper, A. L.; Zeni, A. L. B. Ethnobotanical Study of Plants Used for Therapeutic Purposes in the Atlantic Forest Region, Southern Brazil. *J. Ethnopharmacol.* **2015,** *164*, 136–146.

Tuler, A. C.; da Silva, N. C. Women's Ethnomedicinal Knowledge in the Rural Community of São José da Figueira, Durandé, Minas Gerais, Brazil. *Rev. Bras. Farmacogn.* **2014,** *24* (2), 159–170.

Valverde, S. S.; Santos, B. C. S.; de Oliveira, T. B.; Gonçalves, G. C.; de Sousa, O. V. Solidagenone from *Solidago chilensis* Meyen Inhibits Skin Inflammation in Experimental Models. *Basic Clin. Pharmacol. Toxicol.* **2021,** *128* (1), 91–102.

Valverde, S. S.; Souza, S. P. D.; Oliveira, T. B. D.; Kelly, A. M.; Costa, N. F.; Calheiros, A. S.; et al. Chemical Composition and Antinociceptive Activity of Volatile Fractions of the Aerial Parts of *Solidago chilensis* (Compositae). *Rodriguésia*, **2020,** *71*.

Vechia, C. A. D.; Morais, B.; Schonell, A. P.; Diel, K. A. P.; Faust, C.; Menin, C.; et al. Isolamento químico e validação analítica por cromatografia líquida de alta eficiência de quercitrina em *Solidago chilensis* Meyen (Asteraceae). *Rev. Bras. Plantas Med.* **2016,** *18* (1), 288–296.

Vila, R.; Mundina, M.; Tomi, F.; Furlán, R.; Zacchino, S.; Casanova, J.; Cañigueral, S. Composition and Antifungal Activity of the Essential Oil of *Solidago chilensis*. *Planta Med.* **2002,** *68* (02), 164–167.

Vogas, R. S.; Pereira, M.; Duarte, L. S.; Carneiro, M. J.; Farsura, A. F.; Machado, J. A. M.; et al. Evaluation of the Anti-Inflammatory Potential of *Solidago microglossa* (Arnica-brasileira) In Vivo and Its Effects on PPARγ Activity. *An. Acad. Bras. Ciênc.* **2020,** *92* (2), e20191201.

Zampini, I. C.; Cudmani, N.; Islas, M. I. Actividad antimicrobiana de plantas medicinales argentinas sobre bacterias antibiótico-resistentes. *Acta Bioquímica Clínica Latinoamericana* **2007,** *41* (3), 385–393.

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CHAPTER 3

Therapeutic Properties of *Strychnos nux-vomica* L.

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ABSTRACT

Strychnos nux-vomica L. is native to Asian countries. The vast therapeutic properties of the *S. nux-vomica* had always attracted scientific interest. The seed of the plant that is rich in various phytocompounds of therapeutic importance. HPTLC technique had shown the existence of tannin, alkaloid, carbohydrate, triterpenoid, steroid, and glycoside in the hydroalcoholic extract of the plant seeds. The plant extract has various therapeutic properties like anti-inflammatory, analgesic, and antiallergic and antimicrobial activity.

3.1 INTRODUCTION

Strychnos nux-vomica L. is a shrub of family Loganiaceae, and is native to Asian countries including Sri Lanka, India, China, and Oceania continent Australia. It usually attains the height of 5–25 m. The leaves are opposite to each other with decussate arrangement and are papery, with suborbicular blade (Guo et al., 2018). The ripe fruit pod with maximum of five seeds is hard when dried with around 1.5–3 cm diameter and 3–6 mm thickness. The embryo is housed in horny endosperm, usually grey in color and have bitter taste but no odor (Guo et al., 2018). In India, the plant is known as kuchla (Bhati et al., 2012).

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Being a commonly used plant in Chinese herbal medicine, the plant is well documented in the pharmacopeia of China for its therapeutic properties including treatment of diabetes, asthma, aphrodisiac, and to improve appetite, along with alleviating pain and swelling (Bhati et al., 2012; Guo et al., 2018).

Owing to the diversities of phytoconstituents present in the plant, it had been validated for treatment of various disorders including cancer, cardiovascular diseases, inflammatory responses, and infection from microbial pathogens (Patel et al., 2017). It is the seed of the plant that is rich in various phytocompounds of therapeutic importance, and is called Nux vomica. The plant regulates the peristaltic movement of bowel associated with nutrient absorption. Such important action helps in preventing diarrhea. However, such studies are limited to animals and not human.

The plant is having extensive and diverse use in South Asian subcontinent, especially India. According to reports from Kumar and Sinha (2009), nux vomica is utilized in more than 60 formulations of Indian systems of medicine of which 30 formulations are used in the disorders of vata dosha (Kumar and Sinha, 2009).

3.2 PHYTOCOMPOUNDS OF *S. NUX-VOMICA*

The phytocompounds in the seeds are also of high therapeutic potential. The seeds extracts are observed to be rich in alkaloids. Some of the major constituents are phytocompounds, strychnine, and brucine (Kumar and Sinha, 2009). Some of the alkaloids present in minor amount in the seeds are protostrychnine, vomicine, n-oxystrychnine, pseudostrychnine, isostrychnine, chlorogenic acid, and a glycoside (Bhati et al., 2012). Maji et al. (2017) had compiled an excellent review on the phytocompounds of the plant their therapeutic potential. Some of the active phytocompounds, isolated from various plant parts and documented are tabulated in Table 3.1.

According to Chinese pharmacopeia, the content of strychnine must be between 1.20% and 2.20%, and brucine equal to or more than 0.80%, in Nux vomica (Guo et al., 2018). Brucine and strychnine are two of the important active phytoconstituents of this plant, which stimulate central nervous system, but are toxic (Kushwaha et al., 2014; Patel et al., 2017). The poisonous compounds are not only limited to the seeds of the plants but are also found in leaves and barks of the tree. Zhao et al. (2016) study on the toxicity of the plant extract on zebrafish showed ill effect on several organs including heart, liver, brain, and kidney. Though *S. nux-vomica* induced cardiotoxicity was

TABLE 3.1 Phytoconstituents of *Strychnos nux-vomica* L, and the Plant Parts from Which They Are Extracted.

S. No	Phytoconstituents	Chemical Nature	Site of localization in plant	Major/Minor phytoconstituents	References
1	Strychnine	Indole alkaloid	Seeds (contain 1.25–1.5%), bark, fruit pericarp	Major	Patel et al. (2012), Sukul et al. (2001)
2	Brucine	Indole alkaloid	Seeds (contain 1.7%), bark	Major	Daniel (2006)
3	Pseudostrychnine	Alkaloid	Seeds	Minor	Kumar and Sinha (2009)
4	Pseudobrucine	Alkaloid	Seeds	Minor	Schmelzer and Gurib-Fakim (2008)
5	β-colubrine	Alkaloid	Seeds	Minor	Kushwaha et al. (2014)
6	α-colubrin	Alkaloid	Seeds	Minor	Iwu (2014)
7	Strychnine N-oxide	Alkaloid	Seeds	Minor	Bhati et al. (2012)
8	Brucine N-oxide	Alkaloid	Seeds	Minor	Galeffi et al. (1979)
9	2-hydroxy-3-methoxystrychnine	Alkaloid	Seeds	Minor	Cai et al. (1998)
10	15-hydroxystrychnine	Alkaloid	Seeds	Minor	Frederich et al. (2004)
11	15-acetoxystrychnine	Alkaloid	Seeds	Minor	Xu et al. (2009)
12	3-hydroxy-α-colubrine	Alkaloid	Seeds	Minor	Zhang et al. (2012)
13	3-hydroxy-β-colubrine	Alkaloid	Seeds	Minor	Shi et al. (2014)
14	Isostrychnine	Alkaloid	Seeds	Minor	Yang et al. (2010)
15	Isobrucine	Alkaloid	Seeds	Minor	Zhao et al. (2012)
16	Isobrucine N-oxide	Alkaloid	Seeds	Minor	Fu et al. (2012)
17	Isostrychnine N-oxide	Alkaloid	Seeds	Minor	Zhang et al. (2003)
18	Icajine	Alkaloid	Seeds	Minor	Bisset and Choudhury (1974)
19	Vomicine	Alkaloid	Seeds	Minor	Bisset et al. (1989)
20	Novacine	Alkaloid	Seeds	Minor	Thambi and Cherian (2015)
21	15-hydroxyicajine	Alkaloid	Seeds	Minor	Biala et al. (1998)
22	3-methoxyicajine	Alkaloid	Seeds	Minor	Monache et al. (1968)
23	Sungucine	Alkaloid	Seeds	Minor	Jonville et al. (2013)
24	Isosungucine	Alkaloid	Seeds	Minor	Baser et al. (1979)
25	Protostrychnine	Alkaloid	Seeds	Minor	Baser and Bisset (1982)
26	Diaboline	Alkaloid	Seeds	Minor	Quirin et al. (1965)

reversible to some extent. Study from Ponraj et al. (2017) had reported the mild strychnine poisoning in patient with bradycardia. Studies by Cai et al. (1998) had reported that the IC_{50} of processed seeds were relatively higher than the unprocessed seeds in cell growth-inhibition assay against Vero cells.

The vast therapeutic properties of the *S. nux-vomica* had always attracted scientific interest. Studies by Patel et al. (2012), using HPTLC technique, had shown the existence of tannin, alkaloid, carbohydrate, triterpenoid, steroid, and glycoside in the hydroalcoholic extract of the plant seeds. As per US Pharmacopeia, the alkaloid content should not be <2.5% in the formulation of *S. nux-vomica* (Li et al., 1996). It is the alkaloids along with other phytocompounds that make this plant a well-accepted medicinal plant for alleviating various health problems. The two major alkaloids that are often poisonous in high concentrations are brucine and strychnine (Fig. 3.1). Studies by Shu et al. (2013) had revealed brucine dramatically repressed cell migration with few cytotoxic effects. Hypoxia-inducible factor 1 (HIF-1) is a key transcription factor mediating cell migration and invasion. Brucine plays important role in suppressing HIF-1-dependent luciferase activity in hepatocyte carcinoma cells. The transcription of fibronectin, matrix metallopeptidase 2, lysyl oxidase, and cathepsin D that are HIF-1 target genes is also attenuated after brucine treatment. Experiments involving *Strychnos* had also shown dose-dependent decrease in the lung metastasis of hepatic tumor cells (Shu et al., 2013)

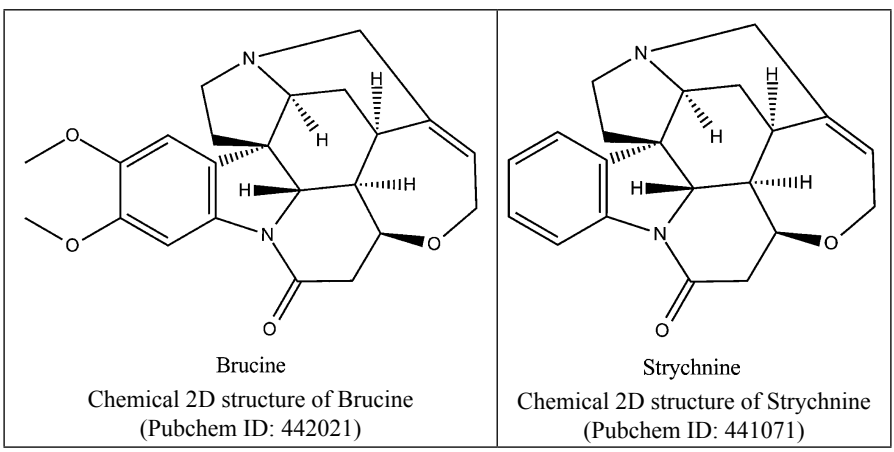

FIGURE 3.1 Chemical structure of the two poisonous alkaloids of *Strychnos nux-vomica*, (a) Brucine, and (b) Strychnine (drawn by the author).

3.3 THERAPEUTIC PROPERTIES OF PHYTOCOMPOUNDS

3.3.1 ANTIMICROBIAL ACTIVITY OF PLANT EXTRACT

Inhibitory effect of the plant extract had been found on both, Gram-positive bacteria and Gram-negative bacteria. Studies from Thavamani and Sreeramulu (1994) had shown concentration-dependent antimicrobial activities against *Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Aeromonas hydrophila, Pseudomonas aeruginosa, Salmonella typhi*, and *Pseudomonas marginalis* at different concentrations (Thavamani and Sreeramulu, 1994). Studies by Mishra et al. (1992) had shown that organic and inorganic extracts of the plant were effective against six pathogenic strains of rice namely *Fusarium moniliforme, Pyricularia oryzae, Curvularia lunata, Rhizoctonia solani, Aspergillus niger*, and *Aspergillus flavus*. The study involves extraction of the phytocompounds in aqueous extract from the plant parts and qualitative analysis of microbial growth. The results may be extended to develop a formulation for preventing impact on plant. Studies by Hofbauer et al. (2010) revealed suppressive effect of alcoholic extract of the seeds of plant against *Helicobacter pylori* induced upregulated heparin-binding epidermal growth factor. Studies were not only limited to seed extract, but extended to flower extracts also. Study from Mohesh et al. (2015) had reported antimicrobial activities in flow extract also against *Klebsiella pneumoniae* and *Candida albicans*.

3.3.2 ANTI-INFLAMMATORY, ANALGESIC, AND ANTIALLERGIC PROPERTY

Various studies have been done on the anti-inflammatory properties of the alkaloids present in *S. nux-vomica***.** Investigation of the anti-inflammatory activities of brucin and brucin N-oxide had shown that both are inhibiting prostaglandin E2 (PGE2) and increased content of 5-hydroxytryindole-3-acetic acid (5-HIAA) (Chaurasia et al., 1995; Wu et al., 2003). Studies from Chen et al. (2012) had reported the anti-inflammatory and analgesic activity attributed to higher fraction of brucine than strychnine in the alkaloid extract of the plant. Brucine was also reported for higher transdermal absorption from the extract than the pure compound.

Duddukuri et al. (2008) reported the suppressive role of plant extract on allergen-specific IgG antibodies. Yin et al. (2003) also reported the analgesic

and anti-inflammatory effect in the seed extract rich in brucine and brucine N-oxide.

3.3.3 EFFECT OF PLANT EXTRACT AGAINST DIABETES MELLITUS

Studies from Chitra et al. (2010) had shown antidiabetic potential of the alcoholic extract of the plant. Detailed analysis showed the effect of plant extract increased catalase, superoxide dismutase and total protein level and decreased lipid peroxidation, suggesting the potential of phytocompounds rich plant extract in regulating Diabetes mellitus. Mathivanan et al. (2014) also highlighted antidiabetic and antioxidant activity of the plant extract, evaluated using biochemical and alpha-amylase inhibition studies.

3.3.4 EFFECT OF PLANT EXTRACT ON CENTRAL NERVOUS SYSTEM

The detailed analysis of plant extract on alleviating the symptoms and regulating the progression of CNS diseases had shown that the phytocompound "loganin" is involved in conferring neuroprotective properties. Moreover, the plant extract when administered in mice model, repressed acetylcholinesterase activity in the frontal cortex and hippocampus (Kwon et al., 2009; Kanika et al., 2017). Studies in mice model showed that impairments in memory and learning, analyzed using the passive avoidance, Y-maze, and the Morris water maze tests in mice notably improved memory impairment in the SNV treated group, in comparison to control. The loganin appreciably inhibited acetylcholinesterase activity in the frontal cortex and hippocampus. Loganin may have antiamnesic activity that may hold significant therapeutic value in alleviating memory disablement observed in Alzheimer's disease (Kwon et al., 2009; Kanika et al., 2017).

3.3.5 EFFECTS OF PLANT EXTRACT ON CELL LINE

Effect of Sandhika, a polyherbal formulation containing *S. nux-vomica* plant extract as main ingredients has been tested on osteoblast-like cells. Result showed that lipopolysaccharides induced anabolic effect on osteoblast-like cells (Tripathi et al., 2008)

3.3.6 EFFECTS OF PLANT EXTRACT ON CARDIOVASCULAR SYSTEMS

Studies from Tripathi et al. (2005), on exploring the effect of polyherbal formulation "Bhux" on albino rabbits obtrude the herbal formulation as a potent multifactorial formulation against atherosclerosis. However, studies on the phytocompounds involved and their role in alleviating the symptom of cardiovascular diseases have not been explored in detail.

The vast therapeutic potentials, reported for the plant are more significant than the toxicity shown by plants due to alkaloids. Strychnine, the alkaloid primarily responsible for toxicity of the plant extract was drastically reduced depending on extraction procedure (Akbar et al., 2010).

3.3.7 HEPATOPROTECTIVE ACTIVITY

The plant extract had also been explored for its hepatoprotective effect. Tripathi and Chaurasia (1996) reported the role of alcoholic extract of plant on lipid peroxidation in liver. Visen et al. (1998) explored the hepatoprotective effect of loganin against glucosamine-induced hepatic damage. Studies by Gopalkrishna et al. (2010), involved processing the seed by following the procedure mentioned in ancient Indian literature Ayurveda with modification for detoxification, or in other words removing phytocompounds known for their toxic effect (Mitra et al., 2011). Soaking the seeds in cow milk, followed by boiling in cow milk and fried process in cow ghee considerably reduced the amount of strychnine and brucine in the extract. The extract was efficacious against CCl_4-induced hepatotoxicity in rats (Gopalkrishna et al., 2010).

3.3.8 OTHER THERAPEUTIC PROPERTIES

The plant system had attracted scientific interest, because of phytocompounds regulated other therapeutic activities also. Cai et al. (1996) reported the role of crude alkaloids extracts from the dried seeds of *S. nux-vomica*, toward antinociceptive effect. The plant-derived metabolites have proved time and again to be more efficacious to the synthetic counterparts that are often reported for their side effects.

Chatterjee et al. (2004) proposed the seed extract (ethanolic) as potential polyvalent snake venom antiserum. The study highlight the role of extract

in neutralizing venom-induced haemorrhage, defibrinogenating, cardiotoxic, neurotoxic, and PLA2 enzyme activity. The phytocompounds of the plant have also been explored for antitumor effects. Detailed studies by Deng et al. (2006), comparing the antitumor properties of four different alkaloids in the seed extracts namely brucine, strychnine, brucine N-oxide, and isostrychnine, revealed better efficacy of strychnine, brucine, and isostrychnine against HepG2 cell proliferation. Brucine was further evaluated to cause cell death via apoptosis. Zheng et al. (2013) reported the apoptotic effect of brucine against LoVo cells.

KEYWORDS

- ***Strychnos nux-vomica***
- **phytotherapeutic**
- **anti-inflammatory**
- **phytocompounds**
- **extract**

REFERENCES

Akbar, S.; Khan, S. A.; Masood, A.; Iqbal, M. Use of *Strychnos nux-vomica* (Azraqi) Seeds in Unani System of Medicine: Role of Detoxification. *Afr. J. Tradit. Complement. Altern. Med.* **2010,** *7*, 286–290.

Baser, K. H. C.; Bisset, N. G. Alkaloids of Sri Lankan *Strychnos nux-vomica*. *Phytochemistry* **1982,** *21*, 1423–1429.

Baser, K. H. C.; Bisset, N. G.; Hylands, P. J. Protostrychnine, a New Alkaloid from *Strychnos nux-vomica*. *Phytochemistry* **1979,** *16*, 512–524.

Bhati, R.; Singh, A.; Saharan, V. A.; Ram, V.; Bhandari, A. *Strychnos nux-vomica* Seeds: Pharmacognostical Standardization, Extraction, and Antidiabetic Activity. *J. Ayurveda Integr. Med.* **2012,** *3* (2), 80–84. DOI: 10.4103/0975-9476.96523.

Biala, R. G.; Tits, M.; Penelle, J. Strychnochrysine, a New Bisindole Alkaloid from the Roots of *Strychnos nux-vomica*. *J. Nat. Prod.* **1998,** *61*, 139–141.

Bisset, N. G.; Choudhury, A. K. Alkaloids and Iridoids from *Strychnos nux-vomica* Fruits. *Phytochemistry* **1974,** *13*, 265–269.

Bisset, N. G.; Choudhury, A. K.; Houghton, P. J. Phenolic Glycosides from the Fruit of *Strychnos nux-vomica*. *Phytochemistry* **1989,** *28*, 1553–1554.

Cai, B.; Nagasawa, T.; Kadota, S.; et al. Processing of Nux Vomica. VII. Antinociceptive Effects of Crude Alkaloids from the Processed and Unprocessed Seeds of *Strychnos nux-vomica* in Mice. *Biol. Pharm. Bull.* **1996,** *19*, 127–131.

Cai, B. C.; Wang, T. S.; Kurokawa, M. Cytotoxicities of Alkaloids from Processed and Unprocessed Seeds of *Strychnos nux-vomica. Acta Pharmacol. Sin.* **1998,** *19*, 425–428.

Chatterjee, I.; Chakravarty, A. K.; Gomes, A. Antisnake Venom Activity of Ethanolic Seed Extract of *Strychnos nux vomica* Linn. *Indian J. Exp. Biol.* **2004,** *42*, 468–475.

Chaurasia, S.; Tripathi, P.; Tripathi, Y. B. Antioxidant and Antiinflammatory Property of Sandhika: A Compound Herbal Drug. *Indian J. Exp. Biol.* **1995,** *33*, 428–432.

Chen, J.; Wang, X.; Qu, Y. G. Analgesic and Anti-Inflammatory Activity and Pharmacokinetics of Alkaloids from Seeds of *Strychnos nux-vomica* After Transdermal Administration: Effect of Changes in Alkaloid Composition. *J. Ethnopharmacol.* **2012,** *139*, 181–188.

Chitra, V.; Varma, P. V.; Raju, K. A. Study of Antidiabetic and Free Radical Scavenging Activity of the Seed Extract of *Strychnos nux-vomica*. *Int. J. Pharm. Pharm. Sci.* **2010,** *2*, 106–10.

Daniel, M. *Medicinal Plants: Chemistry and Properties*; Science Publishers, 2006.

Deng, X. K.; Yin, W.; Li, W. D. The Anti-Tumor Effects of Alkaloids from the Seeds of *Strychnos nux-vomica* on HepG2 Cells and Its Possible Mechanism. *J. Ethnopharmacol.* **2006,** *106*, 179–186.

Duddukuri, G. R.; Brahmam, A. N.; Rao, D. N. Suppressive Effect of *Strychnos nux-vomica* on Induction of Ovalbumin-Specific IgE Antibody Response in Mice. *Indian J. Biochem. Biophys.* **2008,** *45*, 341–344.

Frederich, M.; Choi, Y. H.; Angenot, L. Metabolomic Analysis of *Strychnos nux-vomica, Strychnos icaja* and *Strychnos ignatii* Extracts by 1H Nuclear Magnetic Resonance Spectrometry and Multivariate Analysis Techniques. *Phytochemistry* **2004,** *65*, 1993–2001.

Fu, Y.; Zhang, Y.; He, H. Strynuxlines A and B, Alkaloids with an Unprecedented Carbon Skeleton from *Strychnos nux-vomica*. *J. Nat. Prod.* **2012,** *75*, 1987–1990.

Galeffi, C.; Nicoletti, M.; Messana, I. On the Alkaloids of *Strychnos*—XXXI. 15-Hydroxystrychnine, a New Alkaloid from *Strychnos nux vomica* L. *Tetrahedron* **1979,** *35*, 2545–2549.

Gopalkrishna, S. V.; Lakshmi, N. M.; Ramachandra, S. S. Hepatoprotective Activity of Detoxified Seeds of Nux-Vomica Against CCl_4 Induced Hepatic Injury in Albino Rats. *Pharmacologyonline* **2010,** *1*, 803–815.

Guo, R.; Wang, T.; Zhou, G.; Xu, M.; Yu, X.; Zhang, X.; et al. Botany, Phytochemistry, Pharmacology and Toxicity of *Strychnos nux-vomica* L.: A Review. *Am. J. Chin. Med.* **2018,** *46* (1), 1–23.

Hofbauer, R.; Pasching, E.; Moser, D. Heparin-Binding Epidermal Growth Factor Expression in KATO-III Cells After *Helicobacter pylori* Stimulation Under the Influence of *Strychnos nux-vomica* and *Calendula officinalis*. *Homeopathy* **2010,** *99*, 177–182.

Iwu, M. M. *Handbook of African Medicinal Plants*; 2nd ed.; CRC Press, 2014.

Jonville, M. C.; Dive, G.; Angenot, L. Dimeric Bisindole Alkaloids from the Stem Bark of *Strychnos nuxvomica* L. *Phytochemistry* **2013,** *87*, 157–163.

Kanika, P.; Damiki, L.; Gireesh, K. S.; Manoj, G.; Dinesh, K. P. A Review on Medicinal Uses, Analytical Techniques and Pharmacological Activities of *Strychnos nuxvomica* Linn.: A Concise Report. *Chin. J. Integr. Med.* **2017**.

Kumar, A.; Sinha, B. N. Ayurvedic Processing of Nux Vomica: Qualitative and Quantitative Determination of Total Alkaloidal Contents and Relative Toxicity. *Malay. J. Pharm. Sci.* **2009,** *7*, 83–98.

Kushwaha, R. K.; Berval, R.; Sharma, A. The Therapeutic and Toxicological Effect of Kupilu (*Strychnos nux-vomica* L.)—A Review. *Ayushdhara* **2014,** *1*, 1–4.

Kwon, S. H.; Kim, H. C.; Lee, S. Y.; Jang, C. G. Loganin Improves Learning and Memory Impairments Induced by Scopolamine in Mice. *Eur. J. Pharmacol.* **2009,** *619*, 44–49.

Li, P. T.; Leeuwenberg, A. J. M. Loganiaceae. In *Flora of China*, 15; Wu, Z.-Y.; Raven, P. H. Eds.; Science Press, Beijing &Missouri Botanical Garden, St. Louis, MO, 1996; pp 320–338.

Maji, A. K.; Banerji, P. *Strychnos nux-vomica:* A Poisonous Plant with Various Aspects of Therapeutic Significance. *J. Basic Clin. Pharm.* **2017,** *8*, S087–S103.

Mathivanan, K.; Rengasamy, D.; Rajesh, V. Phytochemical Potential of *Euphorbia hirta* Linn. and *Strychnos nux-vomica* Linn. with Reference to Antidiabetic and Antioxidant Properties. *Int. J. Pharmacogn. Phytochem. Res.* **2014,** *6*, 1024–1031.

Mishra, M.; Malik, S. S.; Tewari, S. N. Allelopathic Effect of Certain Botanicals Against Six Fungal Pathogens of Rice. In *Proceedings, First National Symposium. Allelopathy in Agroecosystems (Agriculture & Forestry)*, Feb 12–14; CCS Haryana Agricultural University, Hisar-125 004, India, 1992; pp 191–193.

Mitra, S.; Kumar, V.; Ashok, B. K. A Comparative Anti-Inflammatory Activity of Raw and Processed Kupeelu *Strychnos nux-vomica* (Linn.) Seeds on Albino Rats. *Anc. Sci. Life* **2011,** *31*, 73–75.

Mohesh, M. I. G.; Joy, A. L.; Ratchagan, K.; et al. Antibacterial and Antioxidant Activity of *Strychnos nux-vomica* Flower Extract. *J. Chem. Pharm. Res.* **2015,** *7*, 748–752.

Monache, F. D.; de Brovetto, A. G.; Cor, E. The Separation of the Minor Alkaloids of *Strychnos nux vomica* L. *J. Chromatogr.* **1968,** *32*, 78–79.

Patel, D. K.; Patel, K.; Duraiswamy, B. Phytochemical Analysis and Standardization of *Strychnos nux-vomica* Extract Through HPTLC Techniques. *Asian Pac. J. Trop. Dis.* **2012,** *2*, S56-S60.

Patel, K.; Laloo, D.; Singh, G. K.; Gadewar, M.; Patel, D. K. A Review on Medicinal Uses, Analytical Techniques and Pharmacological Activities of *Strychnos nux-vomica* Linn.: A Concise Report. *Chin. J. Integr. Med*. **2017,** 1–13. DOI: 10.1007/s11655-016-2514-1.

Ponraj, L.; Mishra, A. K.; Koshy, M.; Carey, R. A. B. A Rare Case Report of *Strychnos nux-vomica* Poisoning with Bradycardia. *J. Family Med. Prim. Care.* **2017,** *6* (3), 663–665. DOI: 10.4103/2249-4863.222036.

Quirin, M.; Levy, J.; Lemen, J. Alkaloids from Nux Vomica Leaves: *Strychnos nux vomica* L (Loganiaceae). *Ann. Pharm. Fr.* **1965,** *23*, 93–98.

Schmelzer, G. H.; Gurib-Fakim, A. *Plant Resources of Tropical Africa 11, Medicinal Plant 1*; PROTA Foundation, Backhuys Publishers, 2008.

Shi, Y.; Liu, Y.; Ma, S. Four New Minor Alkaloids from the Seeds of *Strychnos nux-vomica*. *Tetrahedron Lett.* **2014,** *55*, 6538–6542.

Shu, G.; Mi, X.; Cai, J.; Zhang, X.; Yin, W.; Yang, W.; Li, Y.; Chen, L.; Deng, X. Brucine, an Alkaloid from Seeds of *Strychnos nux-vomica* Linn., Represses Hepatocellular Carcinoma Cell Migration and Metastasis: The Role of Hypoxia Inducible Factor 1 Pathway. *Toxicol. Lett.* **2013,** *222* (2), 91–101.

Sukul, N. C.; De, A.; Dutta, R. Nux Vomica 30 Prepared with and Without Succussion Shows Anti-Alcoholic Effect on Toads and Distinctive Molecular Association. *Br. Homoeopath J.* **2001,** *90*, 79–78.

Thambi, M.; Cherian, T. Phytochemical Investigation of the Bark of *Strychnos nux-vomica* and Its Antimicrobial Properties. *Pharm. Innov. J*. **2015,** *4*, 70–72.

Thavamani, S.; Sreeramulu, A. Growth Inhibitory Effect of Certain Plant Extracts Against *Pseudomonas marginalis* Inciting Soft Rots. *J. Ecotoxicol. Environ. Monit.* **1994,** *4*, 249–252.

Tripathi, Y. B.; Chaurasia, S. Effect of *Strychnos nux-vomica* Alcohol Extract on Lipid Peroxidation in Rat Liver. *Int. J. Pharmacogn.* **1996,** *34*, 295–299.

Tripathi, Y. B.; Singh, B. K.; Pandey, R. S.; Kumar, M. Bhux: A Patent Polyherbal Formulation to Prevent Atherosclerosis. *Evid. Based Complement. Alternat. Med.* **2005,** *2*, 217–221.

Tripathi, Y. B.; Tripathi, P.; Korlagunta, K.; Chai, S. C.; Smith, B. J.; Arjmandi, B. H. Role of Sandhika: A Polyherbal Formulation on MC3T3-E1 Osteoblast-Like Cells. *Inflammation* **2008,** *31*, 1–48.

Visen, P. K. S.; Saraswat, B.; Raj, K. Prevention of Galactosamine-Induced Hepatic Damage by the Natural Product Loganin from the Plant *Strychnos nux-vomica*: Studies on Isolated Hepatocytes and Bile Flow in Rat. *Phytother. Res.* **1998,** *12*, 405–408.

Wu, Y.; Tianshan, W.; Fangzhou, Y.; Baochang, C. Analgesic and Anti-Inflammatory Properties of Brucine and Brucine N-Oxide Extracted from Seeds of *Strychnos nux-vomica. J. Ethnopharmacol.* **2003,** *88*, 205–214.

Xu, Y. Y.; Si, D. Y.; Liu, C. X. Research on Bioresponse of Active Compounds of *Strychnos nux-vomica* L. *Asian J. Pharmacokinet. Pharmacodyn.* **2009,** *9*, 179–201.

Yang, G. M.; Tu, X.; Liu, L. J. Two New Bisindole Alkaloids from the Seeds of *Strychnos nux-vomica*. *Fitoterapia* **2010,** *81*, 932–936.

Yin, W.; Wang, T. S.; Yin, F. Z. Analgesic and Anti-Inflammatory Properties of Brucine and Brucine N-Oxide Extracted from Seeds of *Strychnos nux-vomica*. *J. Ethnopharmacol.* **2003,** *88*, 205–214.

Zhang, J. Y.; Li, N.; Hu, K. Chemical Constituents from Processed Seeds of *Strychnos nux-vomica. J. Chin. Pharm. Sci.* **2012,** *21*, 187–191.

Zhang, X.; Xu, Q.; Xiao, H. Iridoid Glucosides from *Strychnos nux-vomica*. *Phytochemistry* **2003,** *64*,1341–1344.

Zhao, N.; Li, L.; Liu, J. New Alkaloids from the Seeds of *Strychnos nux-vomica*. *Tetrahedron* **2012,** *68*, 3288–3294.

Zhao, C.; Tian, J.; Wang, J.; Feng, Y.; Ni, Y.; Fan, J.; Wang, C.; Cao, D.; Zou, Q.; Ma, Z.; Lin, R. Zebrafish Model for Assessing Induced Organ Toxicity by *Strychnos nux-vomica*. *J. Tradit. Chin. Med.* **2016,** *36* (4), 522–529.

Zheng, L.; Wang, X.; Luo, W. Brucine, an Effective Natural Compound Derived from Nux-Vomica, Induces G1 Phase Arrest and Apoptosis in LoVo Cells. *Food Chem. Toxicol.* **2013,** *58*, 332–339.

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CHAPTER 4

Phytochemistry and Bioactive Potential of Water Hyssop [*Bacopa monnieri* (L.) Wettst.]

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ABSTRACT

Bacopa monnieri, also known as brahmi, belongs to the family Plantaginaceae. The plant is widely used as a memory enhancer and neuroprotective in ayurvedic system of medicine. It is a glabrous, creeping herb, perennial and commonly known as water hyssop. The bioactive constituents present in the plant are bacoside A, bacoside B, bacopa saponin C, bacogenin A, cucurbitacin B, bacosine, stigmasterol, brahmine, brahmic acid, apigenin, nicotine, ursolic acid, β-sitosterol, ascorbic acid and stearic acid. The pharmacological activities are neuroprotective, antidepressant, antiepileptic, antioxidant, anti-inflammatory, antidiabetic, improves cognitive function, anxiolytic effect, anticancer, antidiabetic, antimicrobial, vasodilator and hepatoprotective. The plant leaves are used as nerve tonic and nootropic booster. Brahmi is used as a therapeutic agent for treating various diseases such as Alzheimer's disease, neurological disorders, memory related disorders, digestive disorders, asthma, bronchitis and rheumatism. The chapter deals with the phytochemical constituents, structures and their pharmacological activities. The plant parts are used as a rejuvenator for brain and nervous system.

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4.1 INTRODUCTION

Bacopa monnieri (L.) Wettst. belongs to the family Plantaginaceae. It is commonly known as brahmi, bacopa, Indian pennywort, thyme-leaf gratiola, herb of grace, and water hyssop. The synonyms of the plant include *Lysimachia monnieri* L., *Bramia monnieri* (L.) Pennell, *Moniera cuneifolia* Michx, and *Gratiola monnieri* (L.) L. It is a perennial, prostrate herb of 5–30 cm long, rooting at nodes. The stems are pale yellowish green with a purplish tinge and leaves decussate, ovate-oblong. The flowers are blue or white with a purple tinge, about 0.6–3 cm in length. Fruits are about 5 mm in length. The seeds are numerous and very tiny, irregular, and less than 1 mm wide. It is paleotropical in distribution.

B. monnieri is a famous Indian medicinal herb used to improve intelligence and reduce mental deficits. It is used as a memory enhancer in vedic and ayurvedic medicine since ancient ages. It is used to treat neurological disorders, gastroesophageal reflux, improve concentration, and learning abilities. It also provides relief to patients with dermatological disorders, anxiety, insanity, asthma, and epilepsy (Sukumaran et al., 2019). This nootropic herb helps in neurological synthesis, restoration of injured neurons, improves brain function, and rehabilitation of synaptic activity (Rajani, 2008).

4.2 BIOACTIVE COMPOUNDS

The bioactive compounds of *B. monnieri* include alkaloids, steroids, terpenoids, phytosterols, fatty acids, and saponins (Table 4.1). The first isolated compound in *Bacopa* is "brahmine," which is an alkaloid (Saha et al., 2020). This is used as a medicinal plant having several uses; one among them is "memory enhancing agent" which is an enriched phytochemicals obtained from *B. monnieri* (Allan et al., 2007) (Fig. 4.1).

The bioactive compounds in *B. monnieri* includes brahmine, nicotine, nicotinine, bacoside A & B, bacopa saponin A–G; D-mannitol, bacopaside-I, bacopaside-II, bacopaside-III, bacopaside-IV, bacopaside-V, bacopaside-VI, plantainoside B, betulinic acid, apigenin, herpestine, stearic acid, cucurbitacin A–E, rosavin, ursolic acid, 3,4 dimethoxy cinnamic acid, α-alanine, D-mannitol, ascorbic acid, asiatic acid, brahmic acid, wogonin, luteolin, oroxindin, loliolide, dotriacontane, stigmasterol, β-sitosterol, ebelin lactone, stigmastnol, bacosterol, bacosine, heptacosane, octacosane, nonacosane, triacontane, hentriacontane, dotriacontane, pseudo-jujubogenin glycoside and quercetin (Deepak et al., 2005; Allan et al., 2007; Hou et al., 2002; Jain et al., 2017; Jeyasri et al., 2020). The chemical structures of these bioactive compounds is shown in Figure 4.1. It also consists of isolated triterpenoid compounds such as Bacaposide IX, Bacaposide XI, Bacaposide XII, and apigenin (Zhou et al., 2009; Bhandari et al., 2009).

TABLE 4.1 The Phytochemicals of *B. monnieri* and Their Medicinal Uses.

S. No.	Compounds	Chemical formula	Medicinal uses	References
1.	Apigenin	$C_{15}H_{10}O_5$	Antineoplastic agent; induces autophagy in leukaemia cells	Rohini et al. (2004), Lee et al. (2014)
2.	Brahmic acid	$C_{30}H_{48}O_6$	Anti-inflammatory activity	Won et al. (2010)
3.	Bacoside A	$C_{41}H_{68}O_{13}$	Hepatoprotective, cardioprotective, antioxidant activity	Anbarasi et al. (2006b), Janani et al. (2010)
4.	Bacopaside VII	$C_{46}H_{74}O_{17}$	Antitumor	Peng et al. (2010)
5.	Bacopa saponin A	$C_{40}H_{64}O_{12}$	Antiepileptic	Mathew et al. (2010)
6.	Bacosine	$C_{30}H_{48}O_3$	Antihyperglycemic	Ghosh et al. (2011)a
7.	Bacopa saponin C	$C_{46}H_{74}O_{17}$	Antileishmanial, Nootropic activity	Sinha et al. (2002)
8.	Bacopaside I	$C_{46}H_{74}O_{20}S$	Neuroprotective activity	Sekhar et al. (2019)
9.	Bacopaside II	$C_{47}H_{76}O_{18}$	Anticancer activity	Smith et al. (2018)
10.	Betulinic acid	$C_{30}H_{48}O_3$	Anticancer, antiviral, antimalarial	Pisha et al. (1995), Yogeeswari and Sriram (2005)
11.	Asiatic acid	$C_{30}H_{48}O_5$	Anti-inflammation	Huang et al. (2011)
12.	Ascorbic acid	$C_6H_8O_6$	Antioxidant	Sinha and Saxena (2006)
13.	Stearic acid	$C_{18}H_{36}O_2$	Emulsifying agent	Berg et al. (1990)
14.	Nicotine	$C_{10}H_{14}N_2$	Parkinson's disease; Alzheimer's diseases	Nordberg et al. (2002)
15.	D-Mannitol	$C_6H_{14}O_6$	Used in neurosurgery and neuro ophthalmology	Turliuc et al. (2019)
16.	3,4-dimethoxy cinnamic acid	$C_{11}H_{12}O_4$	Anti-inflammatory activity	Song et al. (2017)
17.	Ursolic acid	$C_{30}H_{48}O_3$	Anticancer activity	Feng and Su (2019), Khwaza et al. (2020)
18.	Bacosterol	$C_{29}H_{50}O$	A secosteroid glycoside	Bhandari et al. (2006)
19.	β-Sitosterol	$C_{29}H_{50}O$	Antioxidant activity	Vats and Tiwari (2014)

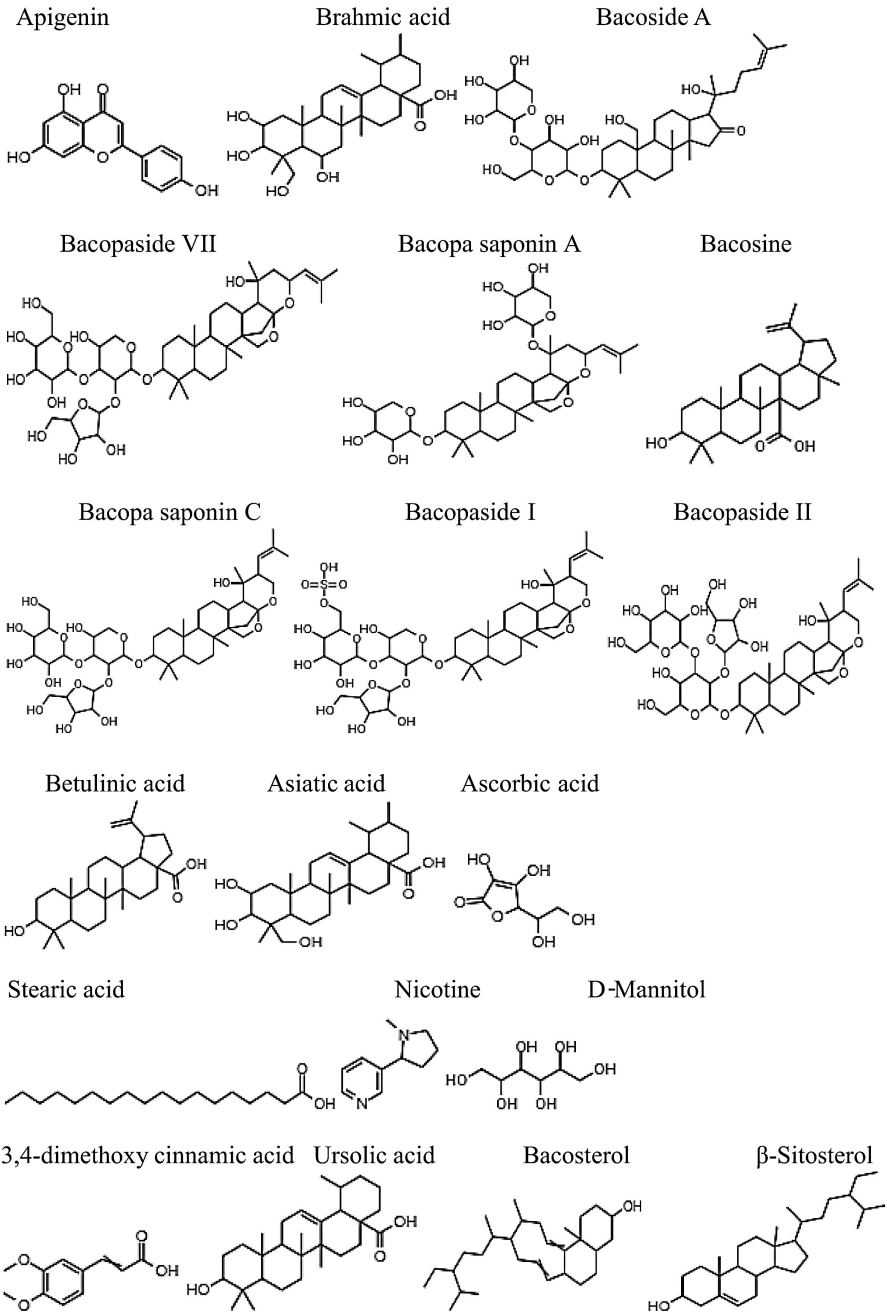

FIGURE 4.1 Chemical structures of bioactive compounds of *B. monnieri*.

4.3 PHARMALOGICAL ACTIVITIES

Bacopa possesses a huge variety of compounds with wide pharmacological importance which includes antianxiety, memory enhancer, antiepileptic, sedative, tranquilizing, antiarthritic, cognitive, antidepressant, antioxidant, gastrointestinal effects, anticancer, antihypertensive, adaptogenic, endocrine, smooth muscle relaxant effects, hepatoprotective, antinociceptive, antipyretic, antidiabetic, antimicrobial, anti-inflammatory, analgesic, neuroprotective, antilipidemia, and cardiovascular activities. The bioactive compounds and their importance are tabulated in Table 4.1. Several mechanisms of action have been proposed for its cognitive effects including neurotransmitter modulation, acetylcholinesterase inhibition, neuroprotection, and β-amyloid reduction (Russo and Borrelli, 2005; Sinha and Saxena, 2006; Bhaskar and Jagtap, 2011).

4.3.1 ANTICANCER/ANTITUMOR ACTIVITY

The genetic disease which arises due to mutations in critical genes is known as "Cancer." It allows the cell to escape from its regular growth and makes it further proliferate leading to a tumor formation (Ghosh et al., 2011b). *B. monnieri* and propolis are natural products that constitute many bioactive compounds possessing anticancer properties. For the treatment of glioblastoma brain tumor, a combination of propolis with *B. monnieri* showed good anticancer activity (Moskwa et al., 2020). Bacoside A, bacoside B, cucurbitacins, betulinic acid, and brahmin are compounds that have shown anticancerous properties (Mallick et al., 2015). The plant extract showed antitumor properties by inducing cell apoptosis on human cell lines. The dammarane diterpenes bacopaside VII and bacopaside E showed antitumor activity against HCT-8, PC-3M, MDA-MB 231, A-549, and SHG-44 cell lines (Peng et al., 2010).

4.3.2 ANTIDIABETIC ACTIVITY

Every year nearly 10% of population get affected by a common metabolic disorder known as diabetes mellitus and hyperglycaemia. The drugs used for treating this disease are insulin and oral hypoglycaemic agents. Various studies reported that these drugs usage possess severe side effects, which lead to increase demand for antidiabetic factor with a little side effects based on medicinal herbal plants. The ethanolic extract of aerial parts decreased

blood glucose levels in diabetic rats compared with the control group of rats. In in-vitro conditions, the glycosylated haemoglobin levels are eliminated (Ghosh et al., 2008). The alcohol and hydroalcoholic extract were evaluated for hyperglycemia and oxidative stress in streptozocin induced diabetes in Wistar rats. The rats were administered with different doses of the extract (100–400 mg/kg) and stigmasterol for 45 days. The serum glucose levels, creatinine, lipid levels, and uric acid levels were monitored and found significant results. The GSH and SOP levels were improved and results in renoprotective effect in diabetic nephropathy (Kishore et al., 2016).

4.3.3 CENTRAL NERVOUS SYSTEM (CNS) ACTIVITY

The ethanolic extract was evaluated for anticonvulsant activity in rats using various convulsive models, such as pentylene tetrazole induced convulsion, maximal electroshock induced convulsion, strychnine induced convulsion, lithium pilocarpine induced status epilepticus, and hypoxic stress induced convulsions. The extract showed anticonvulsive activity against hypoxic, electrical, and chemical convulsions (Kaushik et al., 2009). *B. monnieri* is being used to treat several neurological disorders including epilepsy and showed antiepileptic properties (Komali et al., 2021). The solvent extracts of plant were evaluated for neurotoxicity of pentylene tetrazole in male Wistar rats. Each extract fraction at a dose of 180 mg/kg body weight was administered in animals 1 week preceding to the injection of pentylene tetrazole and compared with diazepam control. The animals were sacrificed and different brain areas are analyzed for acetylcholinesterase activity, acetylcholine content, and ATPases activity. The ATPases and acetylcholinesterase activity were reduced in PTZ-induced epilepsy while the levels were increased in a test group of rats pretreated with extracts of Bacopa plant (Komali et al., 2021).

The alcoholic extract of the plant was evaluated for neurodegeneration and cognitive function in Alzheimer's rat models induced by ethyl choline aziridinium ion (AF64A). The alcoholic extract at a dose of 20, 40, and 80 mg/kg was fed for 2 weeks before and 1 week after administration of AF64A bilaterally. The rats were tested for spatial memory and the density of neurons was evaluated histopathologically and found that the extract improved escape latency time and mitigated the reduction in neuron densities (Uabundit et al., 2010). The triterpenoid saponins and aglycones were evaluated for cognitive effect. The compounds were docked into the active site of receptors D_1, D_2, M_1, 5-HT_1A, and 5-HT_2A and acetyl cholinesterase using autodock tools. The studies have revealed the poor molecular properties of bacoside compounds

compared with the glycone derivates showed better binding activities like CNS drugs. In in-vitro studies, the bacosides showed more binding affinity toward D_1 receptors (Ramasamy et al., 2015). The other compound ebeline lactone showed the strongest affinity toward 5-HT_2A and M_1 receptors that play a role in memory and cognition. In vitro and in-silico studies state that the bacoside A aglycones are accountable for the cognitive function in *B. monnieri* (Ramasamy et al., 2015). Amyloid-β and tau-proteins are associated with neuronal dysfunctions that result in Alzheimer's disease. The bacosides A and B, betulinic acid, and bacosaponins are the phytochemicals that play a role in neuroprotection (Dubey and Chinnathambi, 2019). The *B. monnirei* extract promotes cytotoxicity, free radical scavenging activity, protects the cell against DNA damage, protects cholinergic neurons, and reduces anti-cholinesterase activity. Due to the neurocognitive effect, the plant can be used to treat several neurological diseases (Chaudhari et al., 2017).

4.3.4 ANTIOXIDANT ACTIVITY

The antioxidant activity of the *B. monnieri* extract was evaluated in different regions of rat brain. The extract was administered at a dose of 5 and 10 mg/kg of rat for different time periods (7, 14, and 21 days). The SOD, catalase, and GPx levels were increased for extract after 14 and 21 days in all regions of the brain. The standard drug deprenyl at a dose of 2 mg/kg increased catalase, SOD, and GPx levels in striatum and frontal cortex regions but not in hippocampus region after 14 and 21 days of treatment (Bhattacharya et al., 2000). The antioxidant and DNA damage preventive properties were evaluated for *B. monniera* plant. For DPPH assay, the methanol extract showed the IC_{50} value 0.052 and 0.034 mg/mL for hydroxyl radical scavenging activity. The DNA damage was evaluated using pRSETA plasmid grown in *Escherichia coli* and the extract was effective in preventing DNA damage (Anand et al., 2011)

4.3.5 HEPATOPROTECTIVE ACTIVITY

The bacoside-A, one of the bioactive compound of *B. monnieri,* was assessed for hepatoprotective activity in rats. The bacoside-A 10 mg/kg was fed orally for 21 days and after that d-GalN was injected to induce liver injury in rats. The reduced levels of ALP, ALT, AST, gamma-GT, LDH, and 5′ND were observed and the results suggest that the bacoside-A has hepatoprotective activity in rats (Sumathi and Nongbri, 2008).

The plant extract was fed orally with a 200 mg/kg dose daily once for 10 days in rats. The levels of serum marker enzymes AST, ALP, and ALT levels were restored normally and the SOD, GPx, and catalase activities are increased (Menon et al., 2010). Gudipati et al. (2012) investigated the hepatoprotective role of *B. monnieri* in carbon tetrachloride induced hepatotoxicity in albino mice. The SGOT and SGPT levels are restored normally in plant extract treated group of albino mice. The results revealed the hepatoprotective activity against D-galactosamine, nitrobenzene, and carbon tetrachloride-induced hepatotoxicity in in-vitro models.

4.3.6 ANTI-INFLAMMATORY ACTIVITY

The ethanolic extract of *B. monnieri* was investigated for anti-inflammatory activity in carrageenan-induced inflammation in mice and rat models. The extract at a dose of 100 mg/kg was administered intraperitoneally (10 mL/kg) to the mice and inflammation was induced into right paw by subplantar injection of carrageenan (30 μL) after 30 min. After 3 h, the animals were sacrificed and the paw volume was measured and found to be 58 ± 8% for plant compared with aspirin 54 ± 5%. In case of rats, there is a decline in paw edema that was observed at a dose of 50 and 100 mg/kg (Channa et al., 2006).

The methanolic extract (100 mg/kg) showed 82% edema inhibition compared with indomethacin (3 mg/kg) which showed 70% inhibition in carrageenan rat models. The methanolic extract inhibited the levels of cyclooxygenase-2, 5-lipoxygenase, and 15-lipoxygenase (Viji and Helen, 2008). Williams et al. (2014) evaluated the anti-inflammatory activity on cells of innate immune system. Using RAW246.7 macrophage cell lines, the down-regulation of TNF-α and NO levels was observed after treatment with *B. monnieri* extract. The IFN-γ levels are down-regulated and the IL-10 levels are slightly elevated in human blood cells. These results support the management of diseases related to chronic inflammation using *B. monnieri.*

4.3.7 ANTIARTHRITIC ACTIVITY

Viji et al. (2010) investigated the therapeutic efficacy of *B. monnieri* for rheumatoid arthritis disease in arthritis rat model induced by type-II collagen. The arthritis was induced in male Wistar rats and after 14 days the plant extract was administered and continued for 60 days. The plant extract inhibited the swelling of the foot pad and arthritic symptoms. The cyclooxygenase and lipoxygenase levels are inhibited in arthritic rats. The

neutrophils infiltration, serum IgM, and IgG levels were decreased when compared with the control rats. The results showed antirheumatic activity of the *B. monnieri* for treating the rheumatoid arthritis. The plant extract was investigated for antiarthritic activity and found that the activity is due to the presence of bioactives, such as bacosides and triterpenoids. The plant extract at a dose of 2000 μg/mL showed maximum percentage inhibition of membrane stabilization and protein denaturation values 93.67 ± 1.34% and 90.34 ± 0.83%, respectively. The values are compared with standard drug diclofenac sodium and found to be 98.76 ± 1.67% and 96.52 ± 1.25%, respectively (Volluri et al., 2011).

4.3.8 ANALGESIC ACTIVITY

The ethanolic leaf extract was investigated for analgesic activity in mice models induced by acetic acid. The plant extract was administered at a dose of 250 and 500 mg/kg body weight in test group of animals. The positive control group was administered with 25 mg/kg of diclofenac sodium and the negative control group received 10 mg/kg of 1% Tween 80 in water. The extract showed 36.69% and 59.17% of writhing inhibition at a dose of 250 and 500 mg/kg body weight, respectively, compared with diclofenac showed 72.78% inhibition (Hossain et al., 2012).

4.3.9 ANTIDEPRESSANT AND ANTIANXIETY EFFECTS

Sairam et al. (2002) investigated the antidepressant activity of *B. monnieri* in rats by using behavioral despair test and learned helplessness test. The extract (20 and 40 mg/kg) produced a significant antidepressant activity compared with imipramine (15 mg/kg) intraperitoneally. In another study, the compounds bacopaside I, bacopaside II, and bacopa saponin C were administered 50 mg/kg of each for five consecutive days and the immobility time was found to be 75%, 55%, and 63% in forced swimming method, respectively. In the tail suspension method, the immobility time was found to be 615, 38% and 47%, respectively. These compounds have a glycone moiety having antidepressant effect (Zhou et al., 2007).

The anxiolytic activity was investigated for standardized extract of bacoside A (25.5 ± 0.8%) of *B. monniera.* The extract was administered 5–20 mg/kg orally. The tests like open field test, elevated plus maze, novelty suppressed feeding latency, and social interaction were performed. The extract showed dose-related anxiolytic activity compared with lorazepam

given at a dose of 0.5 mg/kg intraperitoneally (Bhattacharya and Ghosal, 1998).

4.3.10 GASTROINTESTINAL EFFECTS

The ethanolic extract of *B. monnieri* was investigated for antiulcerogenic activity by ethanol-induced gastric injury in Swiss albino mice. The plant extract (aqueous, ethanol, and carbon tetra chloride) 200 and 400 mg/kg in 0.2% Tween 80 was administered orally as a pretreatment. After 1 h, the gastric ulcer is induced by using ethanol 0.5 mL/100 g body weight orally. The animals were evaluated for ulcerative index and percentage protection. The results showed that the group treated with carbon tetrachloride has low UI values (200 mg/kg–13.38 ± 0.47; 400 mg/kg–12.75 ± 0.48) and percentage protection values are 8% and 12%, respectively. In the case of aqueous extract, moderate protection was observed against gastric injury and the UI values were found to be 200 mg/kg–11.63 ± 0.38; 400 mg/kg–10.75 ± 0.25 and percentage protection was 20% and 26%, respectively. The ethanol extract showed the lowest gastric damage and high protection against gastric ulcers. The results are found to be 200 mg/kg–3.13 ± 0.38; 400 mg/kg–2.75 ± 0.32 and percentage protection was 78% and 81%, respectively, compared with the omeprazole group the UI values are 20 mg/kg–2.13 ± 0.13 and percentage protection was 85%. This study suggests that the ethanol extract showed significant protection against gastric damage and similar therapeutic efficacy was observed same as to omeprazole (Karim et al., 2020).

4.3.11 ANTIMICROBIAL ACTIVITY

Sampathkumar et al. (2008) investigated the antimicrobial activity of diethyl ether, aqueous, ethanol, and ethyl acetate extracts of *B. monnieri*. The studies reveal that antibacterial activity has been exhibited by diethyl ether against *Staphylococcus aureus* at a concentration of 300 µg/mL and ethyl acetate against *Proteus vulgaris*. The antifungal activity was observed for ethanolic extract against *Aspergillus niger* and *Candida albicans*. The aqueous extract has no inhibitory activity against indicator microorganisms.

In another study, the antibacterial activity was evaluated for both ethanol and aqueous *B. monnieri* extract against periodontogenic bacteria. The MIC, MBC, and time-kill curve assays were performed against *Prevotella inetrmedia*, *Porphyromonas gingivalis*, *Aggregatibacter actinomycetem-comitans,* and *Fusobacteria nucleatum.* The MIC values of ethanolic extract

were ranged from 100 to 0.8 µg/mL with the highest value for *P. gingivalis* and lowest value for *A. actinomycetemcomitans.* The MIC values of aqueous extract were ranged from 50 to 100 µg/mL with 0.4 µg/mL for *A. actinomycetemcomitans.* The MBC value of ethanolic extract was found to be least for *A. actinomycetemcomitans.* For aqueous extract, the highest MBC value was found for *F. nucleatum* (Suresh et al., 2017). Fazlul et al. (2019) evaluated antibacterial and antifungal activity of *B. monnieri* extract against bacterial and fungal indicator organisms. The ethyl acetate extract showed the highest inhibitory activity against *E. coli* and diethyl ether extracts have activity against *S. aureus*. The ethanol extract has high antifungal activity against *C. albicans* and *A. niger* followed by ethyl acetate and diethyl ether extracts. The aqueous extracts have no inhibitory activity against indicator organisms.

4.3.12 CARDIOVASCULAR ACTIVITY

The plant extract was evaluated for its effect on blood pressure and heart rate in anaesthetized rats. The rats were anaesthetized using pentobarbital by intraperitoneally. The cardiovascular parameters are stabilized and the ethanolic plant extract at a concentration of 20, 40, and 60 mg/kg is dissolved in 0.3 mL of sterile water and administered intravenously. The blood pressure was recorded before and during infusion continuously at 1 mL/min. The ethanolic extract showed a dose-dependent decrease in blood pressure and vasorelaxant effects in rats due to release of nitric oxide from endothelium (Kamkaew et al., 2011).

4.3.13 ANTINOCICEPTIVE ACTIVITY

A hydroethanolic extract of *B. monnieri* (BM HE-ext) was examined by Subhan et al. (2010) in comparison with morphine and diclofenac for antinociceptive activity in the acetic acid induced abdominal constriction assay and the hot plate test in mice. Morphine and BM HE-ext produced dose-related activity that was naloxone-reversible in both tests. Diclofenac effects were dose-dependent only in the abdominal constriction assay and they were not naloxone-reversible at a higher dose. The BM HE-ext antinociception was opioidergic in nature and most likely a manifestation of activity against both tonic and acute phasic pain modalities in each of these nociceptive paradigms.

4.3.14 OTHER ACTIVITIES

B. monnieri extract is known to show various antiaging properties as determined by the studies on induced aging mice (Kalamade et al., 2008). It is a memory enhancer and nootropic activities. It can be used for reducing memory impairment. These plant extracts have neuromodulatory and cytoprotective properties. It is well known to reduce oxidative stress and shows anti-Parkinsonian activities from the studies done on model organisms, such as *Caenorhabditis elegans* (Jadiya et al., 2011). It shows protection against various biochemical changes induced due to high cholesterol content and so can be used as antihypercholesterolemic drug and also wound healing properties (Kamesh et al., 2012; Sharath et al., 2010). It shows protective activity against toxins such as cigarette smoke and as an antilipid peroxidative agent (Anbarasi et al., 2006a; Garg et al., 2009).

KEYWORDS

- **Alzheimer's disease**
- ***Bacopa monnieri***
- **bacosides**
- **brahmine**
- **memory enhancer**
- **neuroprotective**

REFERENCES

Allan, J. J.; Damodaran, A.; Deshmukh, N. S.; Goudar, K. S.; Amit, A. Safety Evaluation of a Standardized Phytochemical Composition Extracted from *Bacopa monnieri* in Sprague—Dawley Rats. *Food Chem. Toxicol*. **2007,** *45* (10), 1928–1937.

Anand, T.; Naika, M.; Swamy, M. S. L.; Khanum, F. Antioxidant and DNA Damage Preventive Properties of *Bacopa monniera* (L) Wettst. *Free Radic. Biol. Med.* **2011,** *1* (1), 84–90.

Anbarasi, K.; Kathirvel, G.; Vani, G.; Jayaraman, G.; Devi, C. S. Cigarette Smoking Induces Heat Shock Protein 70 kDa Expression and Apoptosis in Rat Brain: Modulation by Bacoside A. *Neuroscience* **2006a,** *138* (4), 1127–1135.

Anbarasi, K.; Vani, G.; Balakrishna, K.; Devi, C. S. Effect of Bacoside A on Brain Antioxidant Status in Cigarette Smoke Exposed Rats. *Life Sci.* **2006b,** *78* (12), 1378–1384.

Berg, G.; Seech, A. G.; Lee, H.; Trevors, J. T. Identification and Characterization of a Soil Bacterium with Extracellular Emulsifying Activity. *J. Environ. Sci. Health A* **1990,** *25* (7), 753–764.

Bhandari, P.; Kumar, N.; Singh, B.; Kaul, V. K. Bacosterol Glycoside, a New 13, 14-Seco-Steroid Glycoside from *Bacopa monnieri*. *Chem. Pharm. Bull.* **2006,** *54* (2), 240–241.

Bhandari, P.; Kumar, N.; Singh, B.; Singh, V.; Kaur, I. Silica-Based Monolithic Column with Evaporative Light Scattering Detector for HPLC Analysis of Bacosides and Apigenin in *Bacopa monnieri*. *J. Sep. Sci*. **2009,** *32* (15–16), 2812–2818.

Bhaskar, M.; Jagtap, A. G. Exploring the Possible Mechanisms of Action Behind the Antinociceptive Activity of *Bacopa monniera*. *Int. J. Ayurveda Res.* **2011,** *2* (1), 2–7.

Bhattacharya, S. K.; Bhattacharya, A.; Kumar, A.; Ghosal, S. Antioxidant Activity of *Bacopa monniera* in Rat Frontal Cortex, Striatum and Hippocampus. *Phytother. Res.* **2000,** *14* (3), 174–179.

Bhattacharya, S. K.; Ghosal, S. Anxiolytic Activity of a Standardized Extract of *Bacopa monniera*: An Experimental Study. *Phytomedicine* **1998,** *5* (2), 77–82.

Channa, S.; Dar, A.; Anjum, S.; Yaqoob, M. Anti-Inflammatory Activity of *Bacopa monniera* in Rodents. *J. Ethnopharmacol.* **2006,** *104* (1–2), 286–289.

Chaudhari, K. S.; Tiwari, N. R.; Tiwari, R. R.; Shaarma, R. S. Neurocognitive Effect of Nootropic Drug *Brahmi* (*Bacopa monnieri*) in Alzheimer's Disease. *Ann. Neurosci.* **2017,** *24* (2), 111–122.

Deepak, M.; Sangli, G. K.; Arun, P. C.; Amit, A. Quantitative Determination of the Major Saponin Mixture Bacoside A in *Bacopa monnieri* by HPLC. *Phytochem. Anal.* **2005,** *16* (1), 24–29.

Dubey, T.; Chinnathambi, S. Brahmi (*Bacopa monnieri*): An Ayurvedic Herb Against the Alzheimer's Disease. *Arch. Biochem. Biophys.* **2019,** *676*, 108153. DOI: 10.1016/j.abb.2019.108153.

Fazlul, M. K. K.; Deepthi, S.; Irfan, M. Antibacterial and Antifungal Activity of Various Extracts of *Bacopa monnieri*. *Int. J. Pharm. Res.* **2019,** *11* (1), 1698–1702.

Feng, X. M.; Su, X. L. Anticancer Effect of Ursolic Acid via Mitochondria-Dependent Pathways. *Oncol. Lett*. **2019,** *17* (6), 4761–4767.

Garg, A.; Kumar, A.; Nair, A.; Reddy, A. Elemental Analysis of Brahmi (*Bacopa monnieri*) Extracts by Neutron Activation and Its Bioassay for Antioxidant, Radio Protective and Anti-Lipid Peroxidation Activity. *J. Radioanal. Nucl. Chem.* **2009,** *281* (1), 53–58.

Ghosh, T.; Kumar, M. T.; Sengupta, P.; Dash, D. K.; Bose, A. Anti Diabetic and In Vivo Antioxidant Activity of Ethanolic Extract of *Bacopa monnieri* Linn. Aerial Parts: A Possible Mechanism of Action. *Iran. J. Pharm. Res.* **2008,** *7* (1), 61–68.

Ghosh, T.; Maity, T. K.; Singh, J. Antihyperglycemic Activity of Bacosine, a Triterpene from *Bacopa monnieri*, in Alloxan-Induced Diabetic Rats. *Planta Med*. **2011a,** *77* (8), 804–808.

Ghosh, T.; Maity, T. K.; Singh, J. Evaluation of Antitumor Activity of Stigmasterol, a Constituent Isolated from *Bacopa monnieri* Linn Aerial Parts Against Ehrlich Ascites Carcinoma in Mice. *Orient. Pharm. Exp. Med.* **2011b,** *11* (1), 41–49. B

Gudipati, T.; Srivastava, P.; Bhadauria, R.; Prasad, G. B. Hepatoprotective Potential of In Vitro *Bacopa monnieri* (L.) Against Carbon Tetrachloride-Induced Hepatotoxicity in Albino Mice. *Int. J. Pharm. Biol. Sci*. **2012,** *3* (4), 664–672.

Hossain, H.; Howlader, M. S. I.; Dey, S. K.; Hira, A.; Ahmed, A. Evaluation of Analgesic, Anti Diarrhoeal and Cytotoxic Activities of Ethanolic Extract of *Bacopa monnieri* (L). *J. Pharm. Res. Int*. **2012,** *2* (3), 188–196.

Hou, C. C.; Lin, S. J.; Cheng, J. T.; Hsu, F. L. Bacopaside III, Bacopasaponin G, and Bacopasides A, B, and C from *Bacopa monniera*. *J. Nat. Prod.* **2002,** *65* (12), 1759–1763.

Huang, S. S.; Chiu, C. S.; Chen, H. J.; Hou, W. C.; Sheu, M. J.; Lin, Y. C.; Huang, G. J. Antinociceptive Activities and the Mechanisms of Anti-Inflammation of Asiatic Acid in Mice. *Evid. Based Complement Alternat. Med.* **2011,** *2011*, 895857. DOI: doi.org/10.1155/2011/895857.

Jadiya, P.; Khan, A.; Sammi, S. R.; Kaur, S.; Mir, S. S.; Nazir, A. Anti-Parkinsonian Effects of *Bacopa monnieri*: Insights from Transgenic and Pharmacological *Caenorhabditis elegans* Models of Parkinson's Disease. *Biochem. Biophys. Res. Commun*. **2011,** *413* (4), 605–610.

Jain, P.; Sharma, H. P.; Basri, F.; Priya, K.; Singh, P. Phytochemical Analysis of *Bacopa monnieri* (L.) Wettst. and Their Anti-Fungal Activities. *Indian J. Trad. Knowl.* **2017,** *16* (2), 310–318.

Janani, P.; Sivakumari, K.; Geetha, A.; Ravisankar, B.; Parthasarathy, C. Chemo Preventive Effect of Bacoside A on N-Nitroso Diethylamine-Induced Hepatocarcino Genesis in Rats. *J. Cancer Res. Clin. Oncol.* **2010,** *136* (5), 759–770.

Jeyasri, R.; Muthuramalingam, P.; Suba, V.; Ramesh, M.; Chen, J. T. *Bacopa monnieri* and Their Bioactive Compounds Inferred Multi-Target Treatment Strategy for Neurological Diseases: A Cheminformatics and System Pharmacology Approach. *Biomolecules* **2020,** *10* (4), 536. DOI: 10.3390/biom10040536.

Kalamade, V. I.; Pillai, M. M.; Kalamade, I. S. Effect of *Bacopa monniera* (Linn.) on Lipid Peroxidation and Lipofuscinogenesis in Prostate Gland of D-Galactose Induced Aging Mice, *Mus musculus*. *Indian J. Exp. Biol*. **2008,** *46* (7), 547–549.

Kamesh, V.; Sumathi, T. Antihypercholesterolemic effect of *Bacopa monniera* linn. on High Cholesterol Diet Induced Hypercholesterolemia in Rats. *Asian Pac. J. Trop. Med.* **2012,** *5* (12), 949–955.

Kamkaew, N.; Scholfield, C. N.; Ingkaninan, K.; Maneesai, P.; Parkington, H. C.; Tare, M.; Chootip, K. *Bacopa monnieri* and Its Constituents Is Hypotensive in Anaesthetized Rats and Vasodilator in Various Artery Types. *J. Ethnopharmacol*. **2011,** *137* (1), 790–795.

Karim, R.; Khan, A. F.; Yeasmin, R.; Akter, J.; Akter, T. An Evaluation of Hepatoprotective Activity of Aqueous and Ethanolic Extracts of *Bacopa monnieri* (L.) Against Paracetamol-Induced Hepatotoxicity in Swiss Albino Mice. *Eur. J. Biomed.* **2020,** *7* (2), 393–401.

Kaushik, D.; Tripathi, A.; Tripathi, R.; Ganachari, M.; Khan, S. A. Anticonvulsant Activity of *Bacopa monniera* in Rodents. *Braz. J. Pharm. Sci*. **2009,** *45* (4), 643–649.

Khwaza, V.; Oyedeji, O. O.; Aderibigbe, B. A. Ursolic Acid-Based Derivatives as Potential Anti-Cancer Agents: An Update. *Int. J. Mol. Sci.* **2020,** *21* (16), 5920. DOI: 10.3390/ijms21165920.

Kishore, L.; Kaur, N.; Singh, R. Renoprotective Effect of *Bacopa monnieri* via Inhibition of Advanced Glycation End Products and Oxidative Stress in STZ-Nicotinamide-Induced Diabetic Nephropathy. *Ren. Fail*. **2016,** *38* (9), 1528–1544.

Komali, E.; Venkataramaiah, C.; Rajendra, W. Antiepileptic Potential of *Bacopa monnieri* in the Rat Brain During PTZ-Induced Epilepsy with Reference to Cholinergic System and ATPases. *J. Tradit. Complement. Med.* **2021,** *11* (2), 137–143.

Lee, Y.; Sung, B.; Kang, Y. J.; Kim, D. H.; Jang, J. Y.; Hwang, S. Y.; Kim, M.; Lim, H. S.; Yoon, J. Y.; Chung, H. Y.; Kim, N. D. Apigenin-Induced Apoptosis Is Enhanced by Inhibition of Autophagy Formation in HCT116 Human Colon Cancer Cells. *Int. J. Oncol.* **2014,** *44* (5), 1599–1606.

Mallick, M. N.; Akhtar, M. S.; Najm, M. Z.; Tamboli, E. T.; Ahmad, S.; Husain, S. A. Evaluation of Anticancer Potential of *Bacopa monnieri* L. Against MCF-7 and MDA-MB 231 Cell Line. *J. Pharm. Bio Allied Sci*. **2015,** *7* (4), 325–328.

Mathew, J.; Paul, J.; Nandhu, M. S.; Paulose, C. S. *Bacopa monnieri* and Bacoside-A for Ameliorating Epilepsy Associated Behavioral Deficits. *Fitoterapia* **2010,** *81* (5), 315–322.

Menon, B. R.; Rathi, M. A.; Thirumoorthi, L.; Gopalakrishnan, V. K. Potential Effect of *Bacopa monnieri* on Nitrobenzene Induced Liver Damage in Rats. *Indian J. Clin. Biochem*. **2010,** *25* (4), 401–404.

Moskwa, J.; Naliwajko, S. K.; Markiewicz-Zukowska, R.; Gromkowska-Kępka, K. J.; Nowakowski, P.; Strawa, J. W.; Socha, K. Chemical Composition of Polish Propolis and Its Antiproliferative Effect in Combination with *Bacopa monnieri* on Glioblastoma Cell Lines. *Sci. Rep.* **2020,** *10* (1), 1–16.

Nordberg, A.; Hellstrom-Lindahl, E.; Lee, M.; Johnson, M.; Mousavi, M.; Hall, R.; Court, J. Chronic Nicotine Treatment Reduces β-Amyloidosis in the Brain of a Mouse Model of Alzheimer's Disease (APPsw). *J. Neurochem*. **2002,** *81* (3), 655–658.

Peng, L.; Zhou, Y.; Kong, D. Y.; Zhang, W. D. Antitumor Activities of Dammarane Triterpene Saponins from *Bacopa monniera*. *Phytother Res.* **2010,** *24* (6), 864–868.

Pisha, E.; Chai, H.; Lee, I. S.; Chagwedera, T. E.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M. Discovery of Betulinic Acid as a Selective Inhibitor of Human Melanoma That Functions by Induction of Apoptosis. *Nat. Med.* **1995,** *1* (10), 1046–1051.

Rajani, M. *Bacopa monnieri*, a Nootropic Drug. In *Bioactive Molecules and Medicinal Plants*; Ramawat, K., Merillon, J., Eds.; Springer:Berlin, Heidelberg, 2008. https://doi.org/10.1007/978-3-540-74603-4_9.

Ramasamy, S.; Chin, S. P.; Sukumaran, S. D.; Buckle, M. J. C.; Kiew, L. V.; Chung, L. Y. In-Silico and In-Vitro Analysis of Bacoside A Aglycones and Its Derivatives as the Constituents Responsible for the Cognitive Effects of *Bacopa monnieri*. *PLoS One* **2015,** *10* (5), e0126565.

Rohini, G.; Sabitha, K. E.; Devi, C. S. *Bacopa monniera* Linn. Extract Modulates Antioxidant and Marker Enzyme Status in Fibrosarcoma Bearing Rats. *Indian J. Exp. Biol.* **2004,** *42* (8), 776–780.

Russo, A.; Borrelli, F. *Bacopa monniera*, a Reputed Nootropic Plant: An Overview. *Phytomedicine* **2005,** *12* (4), 305–317.

Saha, P. S.; Sarkar, S.; Jeyasri, R.; Muthuramalingam, P.; Ramesh, M.; Jha, S. In Vitro Propagation, Phytochemical and Neuropharmacological Profiles of *Bacopa monnieri* (L.) Wettst: A Review. *Plants* **2020,** *9* (4), 411. DOI: 10.3390/plants9040411.

Sairam, K.; Dorababu, M.; Goel, R. K.; Bhattacharya, S. K. Antidepressant Activity of Standardized Extract of *Bacopa monniera* in Experimental Models of Depression in Rats. *Phytomedicine* **2002,** *9* (3), 207–211.

Sampathkumar, P.; Dheeba, B.; Vidhyasagar, V.; Arulprakash, T.; Vinothkannan, R. Potential Antimicrobial Activity of Various Extracts of *Bacopa monnieri* (Linn.). *Int. J. Pharmacol*. **2008,** *4* (3), 230–232.

Sekhar, V. C.; Viswanathan, G.; Baby, S. Insights into the Molecular Aspects of Neuroprotective Bacoside A and Bacopaside I. *Curr. Neuropharmacol.* **2019,** *17* (5), 438–446.

Sharath, R.; Harish, B. G.; Krishna, V.; Sathyanarayana, B. N.; Swamy, H. K. Wound Healing and Protease Inhibition Activity of Bacoside-A, Isolated from *Bacopa monnieri* Wettest. *Phytother. Res*. **2010,** *24* (8), 1217–1222.

Sinha, J.; Raay, B.; Das, N.; Medda, S.; Garai, S.; Mahato, S. B.; Basu, M. K. Bacopasaponin C: Critical Evaluation of Anti-Leishmanial Properties in Various Delivery Modes. *Drug Deliv*. **2002,** *9* (1), 55–62.

Sinha, S.; Saxena, R. Effect of Iron on Lipid Peroxidation, and Enzymatic and Non-Enzymatic Antioxidants and Bacoside-A Content in Medicinal Plant *Bacopa monnieri* L. *Chemosphere* **2006,** *62* (8), 1340–1350.

Smith, E.; Palethorpe, H. M.; Tomita, Y.; Pei, J. V.; Townsend, A. R.; Price, T. J.; Young, J. P.; Yool, A. J.; Hardingham, J. E. The Purified Extract from the Medicinal Plant *Bacopa monnieri,* Bacopaside II, Inhibits Growth of Colon Cancer Cells In Vitro by Inducing Cell Cycle Arrest and Apoptosis. *Cells* **2018,** *7* (7), 81. DOI: 10.3390/cells7070081.

Song, M. K.; Lee, S. J.; Kang, Y. Y.; Lee, Y.; Mok, H.; Ahn, J. H. Biological Synthesis and Anti-Inflammatory Activity of Arylalkylamine. *Appl. Biol. Chem.* **2017,** *60* (6), 597–602.

Subhan, F.; Abbas, M.; Rauf, K.; Arfan, M.; Sewell, R. D.; Ali, G. The Role of Opioidergic Mechanism in the Activity of *Bacopa monnieri* Extract Against Tonic and Acute Phasic Pain Modalities. *Pharmacol. Online* **2010,** *3*, 903–914.

Sukumaran, N. P.; Amalraj, A.; Gopi, S. Neuropharmacological and Cognitive Effects of *Bacopa monnieri* (L.) Wettst—A Review on Its Mechanistic Aspects. *Complement. Ther. Med*. **2019,** *44*, 68–82.

Sumathi, T.; Nongbri, A. Hepatoprotective Effect of Bacoside-A, a Major Constituent of *Bacopa monniera* Linn. *Phytomedicine* **2008,** *15* (10), 901–905.

Suresh, S.; Sowmya, N. K.; Mehta, D. S. Evaluation of Antibacterial Activity of *Bacopa monnieri* Extract on Periodontogenic Bacteria—An In-Vitro Study. *Saudi J. Oral Dent. Res.* **2017,** *2*, 265–270.

Turliuc, M. D.; Cucu, A. I.; Costachescu, B.; Tudor, R. M.; Papacocea, T.; Bogdanici, C. M.; Carauleanu, A.; Floria, M.; Tanase, D. M.; Costea, C. F. The Use of Mannitol in Neurosurgery and Neuro-Ophthalmology. *Cell. Chem. Technol*. **2019,** *53* (7–8), 625–633.

Uabundit, N.; Wattanathorn, J.; Mucimapura, S.; Ingkaninan, K. Cognitive Enhancement and Neuroprotective Effects of *Bacopa monnieri* in Alzheimer's Disease Model. *J. Ethnopharmacol.* **2010,** *127*, 26–31.

Vats, S.; Tiwari, R. Evaluation of Antioxidant and Antimicrobial Potential of *Bacopa monnieri* L. *Researcher* **2014,** *6* (9), 20–23.

Viji, V.; Helen, A. Inhibition of Lipoxygenases and Cyclooxygenase-2 Enzymes by Extracts Isolated from *Bacopa monniera* (L.) Wettst. *J. Ethnopharmacol*. **2008,** *118* (2), 305–311.

Viji, V.; Kavitha, S. K.; Helen, A. *Bacopa monniera* (L.) Wettst. Inhibits Type II Collagen-Induced Arthritis in Rats. *Phytother. Res*. **2010,** *24* (9), 1377–1383.

Volluri, S. S.; Bammidi, S. R.; Chippada, S. C.; Vangalapati, M. In-Vitro Anti-Arthritic Activity of Methanolic Extract of *Bacopa monniera*. *Int. J. Chem. Environ. Pharm. Res*. **2011,** *2* (3), 156–159.

Williams, R.; Munch, G.; Gyengesi, E.; Bennett, L.; *Bacopa monnieri* (L.) Exerts Anti-Inflammatory Effects on Cells of the Innate Immune System In Vitro. *Food Funct*. **2014,** *5* (3), 517–520.

Won, J. H.; Shin, J. S.; Park, H. J.; Jung, H. J.; Koh, D. J.; Jo, B. G.; Lee, J. Y.; Yun, K.; Lee, K. T. Anti-Inflammatory Effects of Madecassic Acid via the Suppression of NF-Kappa B Pathway in LPS-Induced RAW 264.7 Macrophage Cells. *Planta Med.* **2010,** *76* (3), 251–257.

Yogeeswari, P.; Sriram, D. Betulinic Acid and Its Derivatives: A Review on Their Biological Properties. *Curr. Med. Chem.* **2005,** *12* (6), 657–666.

Zhou, Y.; Peng, L.; Zhang, W. D. A New Triterpenoid Saponin from *Bacopa monniera*. *Chin. Chem. Lett.* **2009,** *20* (5), 569–571.

Zhou, Y.; Shen, Y. H.; Zhang, C.; Su, J.; Liu, R. H.; Zhang, W. D. Triterpene Saponins from *Bacopa monnieri* and Their Antidepressant Effects in Two Mice Models. *J. Nat. Prod.* **2007,** *70* (4), 652–655.

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CHAPTER 5

An Overview on Phytochemistry and Pharmacology of *Anastatica hierochuntica* L.

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ABSTRACT

This chapter is on a monotypic taxon in the family Brassicaceae, *Anastatica hierochuntica* L. commonly known as *Kaff Maryam* (Mary's hand). The plant is used for treating the difficulty in labors, uterine hemorrhage, and to facilitate the expulsion of the dead fetus. The secondary constituents, Anastatin A and B, Naringenin, Eriodictyol, Aromadendrin, (+)- Taxifolin, 3′-O-methylaxifolin, (+)-Epitaxifolin, Silybin, Hierochins A, B, and C were the major known compounds from this plant. A discussion on the pharmacological activities such as antioxidant, antimicrobial, antifungal, hypolipidemic and hypoglycemia, hepatoprotective, nitric oxide inhibitory effects, anti-inflammatory, antimelanogenic, and gastroprotective were highlighted in this chapter elaborately.

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5.1 INTRODUCTION

Anastatica hierochuntica L. is a monotypic taxon that belongs to the family Brassicaceae, commonly known as *Kaff Maryam* (Mary's hand), *Rose of Jericho, Genggam Fatimah* (Friedman and Stein, 1980). This grey winter annual herb is commonly found in the region of Egypt, Iran, Iraq, Jordan, Kuwait, Libya, North Africa Oman, Saudi Arabia, and the United Arab Emirates (Nasir and Ali, 1980; Law et al., 2009; Daur, 2012; Abdulfattah, 2013). The plant is an annual herb, branched from the base with ascending branches; during the extreme temperature season, this plant rolls inwards and looks like a greying-white dry ball and reappeared into its stable structure once in its favorable climate condition (Jacob and Zipporah, 1980; Van Oudtshoom and Van Rooyen, 1999). The plant is used for treating the difficulty in labors, uterine hemorrhage, and to facilitate the expulsion of the dead fetus (Khalifa, 1980; Abou-Mandour and Hartung, 1995; Rizk et al., 2008; Nani, 2009, 2010; Farid and Law, 2009; Knight, 2010; El Ghazali et al., 2010; Sooi and Keng, 2013). Seeds or sometimes leaves of these plants are used as a tea to treat asthma and respiratory diseases, dysentery, colds, fevers, and headaches, as painkillers and emmenagogues, and epilepsy (Mossa et al., 1987). Nowadays, this plant was highly used by people across the globe, and it was treated as a glorious plant for an alternate treatment for metabolic disorders (Shah et al., 2014). Other known potential of this plant in treating gastric disorder, arthritis, mouth ulcers, malaria, and mental depression (Batanouny, 1999; Jaradat, 2005; Sobhy et al., 2011; Daur, 2012; Sooi and Keng, 2013; Shah et al., 2014;). This detailed review on *A. hierochuntica* will focus on the active phytochemicals and their proven pharmacology activities.

5.2 PHYTOCHEMICAL COMPOUNDS OF *A. HIEROCHUNTICA*

Two major compounds, namely, Anastatin A and B were isolated for the first time from the whole plant along with other compounds like Naringenin, Eriodictyol, Aromadendrin, (+)-Taxifolin, 3′-*O*-methylaxifolin, (+)-Epitaxifolin, and Silybin (Fig. 5.1) by Yoshikawa et al. (2003a). Later, Hierochins A, B, and C from methanolic extracts of whole plants with other compounds like (+)-lariciresinol, kaempferol, Luteolin, rutin, β-sitosterol-3-*O*-β-D-glucopyranoside, (+)-dehydrodiconiferyl alcohol, (+)-balanophonin, and evofloin B (Yoshikawa et al., 2003b).

In recent research by AlGamdi et al. (2011) reported that the most flavones such as luteolin-6-C-hexosyl-8-C-pentoside, luteolin-6-C-pentosyl-8-C-hexoside, api-genin-6,7-C-diglucoside (isovitexin-7-*O*-glucoside), apigenin-6-C-

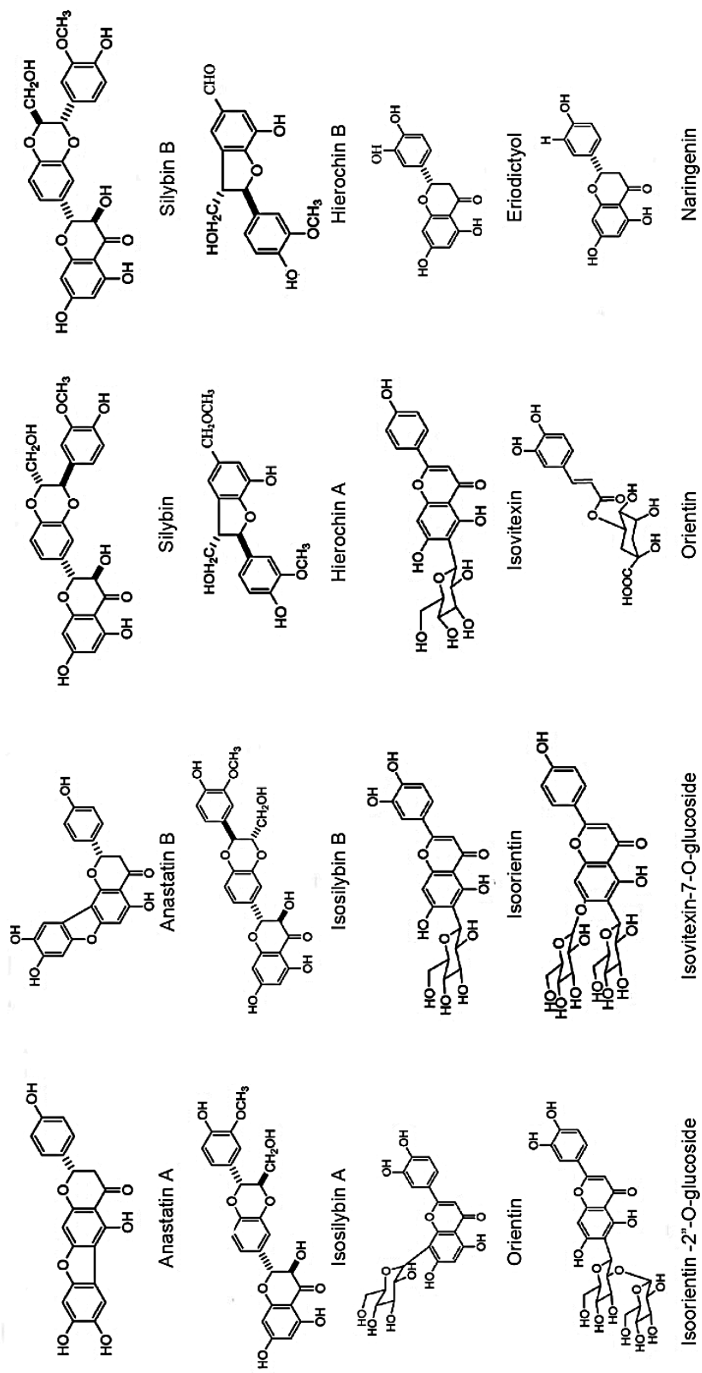

FIGURE 5.1 Class of important phytochemicals isolated from the *A. hierochuntica*.

arabinosyl-8-C-hexoside, luteolin-8-C-glucoside (orientin), luteolin-6-C-glucoside (isoorientin), apigenin-6-C-gluco-side (isovitexin), luteolin-*O*-glucoside, diosmetin-8-C-gluco-side, luteolin-*O*-glucuronide, and luteolin-6-C-glucosyl-2″-*O*-glucoside (isoorientin-2″-*O*-glucoside) (for full list see Table 5.1). Compounds like Kaempferol 3-*O*-(6″-α-*L*-rhamnopyranosyl)-β-D-glucopyranoside; Quercetin 3-*O*-(6″-α-L-rhamnopyranosyl)-β-D-glucopyranoside; Apigenin 6-C-β-D-glucopyranoside (Isovitexin); (+)-Taxifolin (3,5,7,3,4′-Pentahydroxydihydroflavone) along with Quercetin, Isovitexin, and Naringenin were reported by Marzouk et al. (2010). Few earlier reported compounds were once again confirmed by Nakashima et al. (2010) with other phytoconstituents (Table 5.1) and glucose, galactose, fructose, sucrose, raffinose, and stachyose were also found to be present. Lycopene, β-carotene, flavonoids, and phenols were found to be present by Mohamed et al. (2010).

TABLE 5.1 List of Phytochemicals Isolated from *A. hierochuntica.*

Sl. No	Phytochemicals	References
1.	3,4-*O*-dicaffeoylquinic acid	AlGamdi et al. (2011)
2.	4,5-*O*-dicaffeoylquinic acid	AlGamdi et al. (2011)
3.	trans-ferulic acid	Nakashima et al. (2010)
4.	(−)-evofolin B	Nakashima et al. (2010)
5.	(−)-silychristin	Nakashima et al. (2010)
6.	(+) lariciresinol	Yoshikawa et al. (2003b)
7.	(+)-2,3-dihy-droxy-1-(4-hydroxy-3-methoxy-phenyl-1-propanone)	Nakashima et al. (2010)
8.	(+)-30-*O*-methyl taxifolin	Nakashima et al. (2010)
9.	(+)-balanophonin	Yoshikawa et al. (2003b) and Nakashima et al. (2010)
10.	(+)-dehy-drodiconiferyl alcohol	Yoshikawa et al. (2003b) and Nakashima et al. (2010)
11.	(+)-epitaxifolin	Nakashima et al. (2010)
12.	(+)-Epitaxifolin	Yoshikawa et al. (2003a)
13.	(+)-lariciresinol	Nakashima et al. (2010)
14.	(+)-silychristin	Nakashima et al. (2010)
15.	(+)-taxifolin	Nakashima et al. (2010)
16.	(+)-Taxifolin (3, 5, 7,3,4′–Pentahydroxydihydroflavone)	Marzouk et al. (2010)
17.	(+)-Taxifolin, 3′-*O*-methylaxifolin,	Yoshikawa et al. (2003a)
18.	1.8-cineole	Qnais et al. (2017)
19.	2,40-dihydroxy-30-methox-yacetophenone	Nakashima et al. (2010)

TABLE 5.1 *(Continued)*

Sl. No	Phytochemicals	References
20.	3,4-dihydroxybenzaldehyde	Nakashima et al. (2010)
21.	3,4-dihydroxybenzoic acid	Nakashima et al. (2010)
22.	3,4-Dihydroxybenzoic acid	AlGamdi et al. (2011)
23.	3,4-*O*-Dicaffeoylquinic acid	AlGamdi et al. (2011)
24.	3-methoxy-4-hydroxybenzoic acid	Nakashima et al. (2010)
25.	4,5-*O*-Dicaffeoylquinic acid	AlGamdi et al. (2011)
26.	5-*O*-caffeoylquinic acid	AlGamdi et al. (2011)
27.	5-*O*-Caffeoylquinic acid	AlGamdi et al. (2011)
28.	α-agarofuran	Qnais et al. (2017)
29.	α-phellandrene	Qnais et al. (2017)
30.	Acetovanillone	Nakashima et al. (2010)
31.	Amorfene	Qnais et al. (2017)
32.	Anastatin A	Yoshikawa et al. (2003a) and Nakashima et al. (2010)
33.	Anastatin B	Yoshikawa et al. (2003a) and Nakashima et al. (2010)
34.	Apigenin-6-C-arabinosyl-8-C-hexoside,	AlGamdi et al. (2011)
35.	Aromadendrin	Yoshikawa et al. (2003a) and Nakashima et al. (2010)
36.	b-sitosterol-3-*O*-b-D-glucopyranoside	Yoshikawa et al. (2003b)
37.	Coniferaldehyde	Nakashima et al. (2010)
38.	Copaene	Qnais et al. (2017)
39.	Cuminyl acetate	Qnais et al. (2017)
40.	Dihydroxybenzoic acid hexoside	AlGamdi et al. (2011)
41.	Dihydroxybenzoic acid hexoside, 3, 4 dihydroxybenzoic acid	AlGamdi et al. (2011)
42.	Eremoligenol	Qnais et al. (2017)
43.	Eriodictyol	Yoshikawa et al. (2003a) and Nakashima et al. (2010)
44.	Eugenol	Qnais et al. (2017)
45.	Evofolin B	Yoshikawa et al. (2003b)
46.	Germacrene	Qnais et al. (2017)
47.	Hierochin B	Yoshikawa et al. (2003b) and Nakashima et al. (2010)
48.	Hierochin A	Yoshikawa et al. (2003b) and Nakashima et al. (2010)
49.	Hierochin C	Yoshikawa et al. (2003b) and Nakashima et al. (2010)
50.	Humulene	Qnais et al. (2017)
51.	hydroxypropioguaiacone	Nakashima et al. (2010)

TABLE 5.1 *(Continued)*

Sl. No	Phytochemicals	References
52.	Isoorientin	AlGamdi et al. (2011)
53.	Isoorientin-2″-*O*-glucoside	AlGamdi et al. (2011)
54.	Isosilybin A	Nakashima et al. (2010)
55.	Isosilybin B	Nakashima et al. (2010)
56.	Isovitexin	AlGamdi et al. (2011) and Marzouk et al. (2010)
57.	Isovitexin-7-*O*-glucoside	AlGamdi et al. (2011)
58.	Kaempferol	Yoshikawa et al. (2003b) and Nakashima et al. (2010)
59.	Kaempferol 3-*O*-(6″-α-L-rhamnopyranosyl)-β-D-glucopyranoside	Marzouk et al. (2010)
60.	Luteolin	Yoshikawa et al. (2003b) and Nakashima et al. (2010)
61.	Luteolin-6-Chexosyl-8-C-pentoside,	AlGamdi et al. (2011)
62.	Luteolin-6-C-pentosyl-8-C-hexoside,	AlGamdi et al. (2011)
63.	Luteolin-*O*-glucoside, diosmetin-8-C-glucoside	AlGamdi et al. (2011)
64.	Luteolin-*O*-glucuronide.	AlGamdi et al. (2011)
65.	Muurolene	Qnais et al. (2017)
66.	Naringenin	Yoshikawa et al. (2003a), Nakashima et al. (2010), and Marzouk et al. (2010)
67.	p-hydroxybenzaldehyde	Nakashima et al. (2010)
68.	p-hydroxybenzoic acid	Nakashima et al. (2010)
69.	p-methoxybenzoic acid	Nakashima et al. (2010)
70.	Quercetin	AlGamdi et al. (2011), Nakashima et al. (2010), and Marzouk et al. (2010)
71.	Quercetin 3-*O*-(6″-α-L-rhamnopyranosyl)-β-D-glucopyranoside	Marzouk et al. (2010)
72.	Rutin	Yoshikawa et al. (2003b) and Nakashima et al. (2010)
73.	Selinene	Qnais et al. (2017)
74.	Silybin	Yoshikawa et al. (2003a)
75.	Silybin A	Nakashima et al. (2010)
76.	Silybin B	Nakashima et al. (2010)
77.	Transcinnamic acid	Nakashima et al. (2010)
78.	Vanillin	Nakashima et al. (2010)
79.	β-Caryophyllene	Qnais et al. (2017)

5.3 PHARMACOLOGICAL PROPERTIES

A. hierochuntica was known for many traditional practices of treatments in ancient history. The evidence-based therapeutically proven pharmacological properties of this plant were discussed as follows. The dried whole part or aerial plant was largely extracted for the studies and the active compound or crude extracts were used to study the antioxidant, antimicrobial, antifungal, hypolipidemic and hypoglycemia, hepatoprotective, nitric oxide inhibitory effects, anti-inflammatory, antimelanogenic, and gastroprotective activities (Rizk et al., 1985; Yoshikawa et al., 2003a, 2003b; Tayel and El-Tras, 2009; Salah et al., 2011, Daoowd, 2013; Shah et al., 2014; Abou-Elella et al., 2016) activities using in vitro and in vivo studies.

5.3.1 ANTIOXIDANT PROPERTIES

AlGamdi et al. (2011) estimated the phenolic content of the seeds of *A. hierochuntica* using HPLC measured with the Folin–Ciocalteu assay and antioxidant properties of the seeds using the FRAP assay showed that phenolic and flavonoids present in the tea of about of individual compounds ranging from 17 ± 0 to 210 ± 1 μM and have significant antioxidant property. The presence of flavonoids shows antioxidant activity and its impact on human health improvement. The proton radical scavenging action is known as an important mechanism of antioxidants. Mohamed et al. (2010) noted that *A. hierochuntica* is lesser antioxidant properties compared to the *Hyphaene thebaica* and standard of butylated hydroxytoluene and butylated hydroxyanisole. The phenols and flavones are known to be one of the most effective free radical scavengers and antioxidants due to their chelating ability to iron ions, thus the presence of these compounds in the plant will serve in rejuvenating the human body cells (Havsteen, 2002; Soong and Barlow, 2004). The amount of 42.53 mg/g d.w. of flavonoids in methanolic extracts of *A. hierochuntica* is reported by Mohamed et al. (2010), which is equivalent to standard quercetin and the percentages of metal scavenging capacity at 200 μg/mL of methanol extracts of *A. hierochuntica,* found to be 16.72%. Another method of analysis is by using the superoxide anion radical scavenging activity. The inhibition percentage of superoxide radical generation by the plant extracts and comparison with quercetin at 300 μg/mL concentration was found to be 52.61% and 75.31%, for quercetin. Thus, the study concluded that the presence of phenols and flavonoids in this plant was potential for antioxidant properties.

5.3.2 ANTI-INFLAMMATORY ACTIVITY

The anti-inflammatory activity was studied by Rizk et al. (1985) using the chloroform extract of *A. hierochuntica* of 10 mL against the platelet-rich plasma, which showed 100% inhibition of the aggregation of rabbit blood platelets. The mechanisms have shown that the presence of membranes stimulating anti-inflammatory compounds is present in the extracts (Zin et al., 2017). Later studies by Abou-Elella et al. (2016) demonstrated that in vitro human red blood cell membrane were treated with the ethanolic extract and subextracted with its various extraction fractions (water, petroleum ether, EtOAc, and butanol). In total, 100 mg/mL of whole ethanolic extract showed a maximum of 57 ± 14.73%, which was close to that of the standard anti-inflammatory drug, diclofenac sodium of 71.33 ± 2.31%.

5.3.3 ANTIMELANOGENIC ACTIVITY

This activity was explained by Nakashima et al. (2010) that methanolic extract of whole plant *A. hierochuntica* significantly inhibited melanogenesis in theophylline-stimulated murine B16 melanoma 4A5 cells. The results were significant with the inhibitory concentration IC_{50} value of 100 mg/mL. The ethyl acetate-soluble fraction of the methanolic extract was having significant inhibition of melanogenesis, with the value of IC_{50} at a 60 mg/mL dose level.

5.3.4 ANTINOCICEPTIVE EFFECT

Qnais et al. (2017) evaluated the antinociceptive effects of the essential oil isolated from the aerial parts of the *A. hierochuntica*. The study with a test dose of 10, 31.6, 100, 316, and 1000 mg/kg (orally). The EOAH extract showed significance in reducing the pain based on the dose-dependent manner in all conducted experiments, the mechanisms explained by the partial blockage of the EOAH antinociceptive action by naloxone. Based on these findings, Qnais et al. (2017) justify that the part of *A. hierochuntica* can be used in the treatment of various painful conditions.

5.3.5 GASTRIC PROTECTIVE PROPERTY

Shah et al. (2014) showed that the *A. hierochuntica* has a gastro-protective property against the stomach ulcer with a dose depend on maxima of 500 mg/kg +80% ethanol (1 mL/rat) is about 378.56 + 10.57 μg/g of gastric

wall mucus. The isolated compounds from this plant were proven to have antiulcer properties by this study. In the future, this property needs to be the focus of preclinical studies.

5.3.6 HYPOGLYCEMIC AND HYPOLIPIDEMIC ACTIVITY

Hypoglycemia is a condition, where blood sugar (glucose) level is lower than normal. Hypolipidemia is a decrease in the level of lipids in the blood. Thus, both were related to the metabolic disorder, Diabetes Mellitus. Salah et al. (2011) studied in-vivo assay by making Alloxan produce insulin-dependent diabetes animals. The mechanism of this study is by using Alloxan, which induced genetic changes in somatic and germ cells. This will lead to the inhibition in the mitotic index. Alloxan and streptozotocin (STZ) impact in destroying β-cells and causing a significant increase in glucose level in blood. This increase in circulating glucose level is believed to contribute to β-cell dysfunction (Hansen, 1998). The plant-based extracts have been used to treat this condition earlier as well, this researcher group analyses 150 mg/kg methanolic extract of *A. hierochuntica* for 15 days and found that the extract has the potential in controlling this glucose and lipid levels and maintain the blood glucose and lipids in normal level. This action of these drugs could also be due to alternation in membrane fatty acid content, which may affect Na+, K+-ATPase activity, membrane fluidity, and fatty acid content (Sennoune et al., 1999). The alloxan-induced diabetic rats were treated with different concentrations, in that 100 mg/kg methanolic extract treated for 28 days showed the restoration of β-cells of the pancreas, the result was about 74% reduction of glucose levels in the dose-dependent manner (Shaban et al., 2011).

The rats were oral routed with 12.5 mg/bw aqueous extract of *A. hierochuntica* for 2 weeks by Rahmy and El-Ridi (2002). The hypoglycaemic effects were then noted in both nondiabetic and STZ-induced diabetic rats leading to improvements in the pancreatic tissue (Zin et al., 2017).

5.3.7 HEPATOPROTECTIVE ACTIVITY

Inhibitory effects of the MeOH and EtOAc soluble fraction on D-galactosamine (D-GaIN)-induced cytotoxicity in primary cultured mouse hepatocytes shows that Anastatin A and Anastatin B of 46.2 ± 39 and 55.0 ± 0.5 of 30 μM, respectively (Yoshikawa et al., 2003a). In another research article, the same team showed that Hierochin A, B, and C were significant against

the inhibitory effects on nitric oxide production and induction of inducible nitric oxide synthase (Yoshikawa et al., 2003b). Another study by Sobhy et al. (2011) also proved the stronger hepatoprotective activities of the major compound anastatin A and anastatin B than other flavonoids, this was also proven by another study using the same compounds (Eman et al., 2011). El-Sayed et al. (2012) showed that 5% and 10% of *A. hierochuntica* powder for 4 weeks will improve carbon tetrachloride (CCl_4)-induced liver damage of male albino rats.

5.3.8 ANTIMALARIAL ACTIVITY

The antimalarial effects of entire plants were studied against parasitic *Plasmodium berghei* PZZ1/100 strain by Sobhy et al. (2011). The study was done for 4 days screened assay, which showed that both intraperitoneal and oral treatments of plant extracts (50, 100, 200, and 400 UL/kg) suppressed activities in all mice group. The high values were found in the 100 and 200 UL/kg dose of the ethanol extract and 100 UL/kg dose of the chloroform extract. The significant impact of this extract increases the survival time of the mice and decreases the parasitaemias. The aqueous extracts of this plant gave suppression activity at 200 and 400 UL/kg dose range.

5.3.9 IMMUNOSTIMULATORY ACTIVITY

Abdulfattah (2013) and Salah et al. (2011) demonstrated that the *A. hierochuntica* extracts significantly increase the level of IgG, IgA, and IgM in the serum of alloxan-induced diabetic rats. The dose of 100 mg/kg significantly decreased the level of another immunological parameter, adenosine deaminase activity which also plays an important role in the immunostimulatory activity. This possibility is due to the presence of flavone glycosidic components in the extract (Abdulfattah, 2013).

5.3.10 ANTICANCEROUS ACTIVITY

Rameshbabu et al. (2020) used the methanolic and aqueous extracts of *A. hierochuntica* to prove the anticancer properties of these plants against the MCF-breast cancer cells. The result was impressive that the extracts decreased MCF-7 (Michigan Cancer Foundation-7) cell viability in a dose-dependent manner. Using the DNA fragmentation and cleavage of the intrinsic apoptotic pathways, caspase-9, and caspase-3, they showed the

cell death of cancerous cells. The most promising extract was the seed and leaf part of this plant, which up-regulated the expression of pro-apoptotic bax, tumor suppressor TP53 genes, and the cyclin inhibitor CDKN1A gene. Anticervical cancer studies were made by Hajjar et al. (2017) and used automated high-content imaging of cancer active cells. The cluster analyses of the cytological profiles of the *A. hierochuntica* compounds suggested that this plant contains possible topoisomerase inhibitors. They discovered that some of the compounds induced double-strand DNA breaks using histone H2AX phosphorylation as a marker for DNA damage.

5.3.11 MICROBIAL ACTIVITY

The aqueous and ethanolic extracts of *A. hierochuntica* were studied against seven foodborne bacterial strains using paper disc diffusion and agar dilution method by Tayel and El-Tras (2009), thus the result shows that antimicrobial properties of the aqueous extract against *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Pseudomonas fluorescens*, and *Staphylococcus aureus* but the sign is weak as compared to other herbs used in this study. Methanolic and aqueous extracts of *A. hierochuntica* show activities against only *B. subtilis* under Gram-positive bacteria and none under Gram-negative bacteria, fungus, and yeast culture discs that were impregnated with 40 mg/mL extracts (Mohamed et al., 2010). Al Sobeai (2016) studied microbial evaluation of the ethanol, methanol, and aqueous extracts by agar well diffusion method against 10 bacterial pathogens. Among all three extracts, the methanolic extract showed the highest inhibition zone followed by the aqueous and ethanolic extracts. The result value showed that minimum inhibitory concentrations ranged from 15 to 50 mg/mL to inhibit the growth of the tested bacteria *Proteus mirabilis* of 20.3 ± 1.3 mm, *Salmonella typhi* of 18.7 ± 0.9 mm, *Salmonella paratyphi* of 18 ± 0.6 mm, and *Klebsiella pneumoniae* of 18 ± 1.3 mm. Furthermore, the aqueous extract displayed inhibitory effects against *Streptococcus faecalis, Streptococcus pyogenes, Shigella sonnei*, and *Enterococcus faecalis*, with no effect against *Listeria monocytogenes*. But Al-Ghanayem et al. (2018) did some antifungal studies and proved that the extracts (150 mg/mL) showed maximum inhibitory effect toward *Microsporum audouinii* and least against *Aspergillus flavus*. And also, the lower concentration of the extract controls the growth of the *Epidermophyton floccosum* and *Fusarium* sp. Earlier in this study, Daoowd (2013) showed the antifungal activity of methanolic leaf extracts which mostly contain the tannins and flavonoids is the highest activity against *Candida*

albicans, Cryptococcus neoformans, Fusarium oxysporum, and *Penicillium digitatam*. These antifungal properties exhibited by *A. hierochuntica* extracts might be attributed to the presence of either a single or synergistic effect of more than one compound (Zin et al., 2017).

5.3.12 TOXICOLOGICAL ASPECTS

The cytotoxic effect of *A. hierochuntica* was evaluated in vitro using Vero cell lines, from African green monkey kidney cells and the cells were cultured in Dulbecco's modified eagle's medium supplemented with 10% fetal bovine serum. Cells treated with extracts were kept in a medium containing 1% FBS, L-glutamine, and antibiotics and incubated at 37°C with 5% CO_2 for 36 h. The result showed that the effect of extracts was low cytotoxic (>1000 µg/mL) (Al Sobeai, 2016). The mean CC_{50} value of methanol, ethanol, and aqueous extract was lower than 1000 µg/mL.

An acute toxicity screening made by Shah et al. (2014) showed that the mices treated for 24 h were alive with no mortality. But the mice showed less locomotor activity with a 3 g/kg body weight. Their study also showed that chronic toxicity on 40 Swiss albino mice which exposed to 100 mg/kg/day of *A. hierochuntica* ethanol extract in drinking water. The result showed that all the treated mice were healthy and active. The animal parts were not infected or affected by any toxicity during this period of study. The blood analysis indicated that white cells, red blood cells, hemoglobin, and platelets showed no significant deviations. And other parameters in biochemical assay also show no fetal toxicity effects. Rasheed et al. (1997) demonstrated an increased incidence of fetal resorption rate of 11 out of 105 resorptions of the total fetuses examined in the high dose group (4 g/kg). A higher incidence of anencephaly was also reported in the fetuses of mice treated with 0.25, 1, and 4 g/kg.

KEYWORDS

- **Brassicaceae**
- ***Kaff Maryam***
- **monotypic taxon**
- **pharmacology**
- **review**

REFERENCES

Abdulfattah, S. Y. Study of the Immunological Effect of *Anastatica hierochuntica* (Kaff Maryam) Plant Methanolic Extract on Albino Male Mice. *J. Biotechnol. Res. Center*. **2013,** *7* (2), 3–10.

Abou-Elella, F.; Hanafy, E. A.; Gavamukulya, Y. Determination of Antioxidant and Anti-Inflammatory Activities, as well as In Vitro Cytotoxic Activities of Extracts of *Anastatica hierochuntica* (Kaff Maryam) Against HeLa Cell Lines. *J. Med. Plants Res*. **2016,** *10* (7), 77–87.

Abou-Mandour, A. A.; Hartung, W. Tissue Culture of the Desert Plant *Anastatica hierochuntica. Plant Cell Rep.* **1995,** *14*, 657.

AlGamdi, N.; Mullen, W.; Crozier, A. Tea Prepared from *Anastatica hierochuntica* Seeds Contains a Diversity of Antioxidant Flavonoids, Chlorogenic Acids and Phenolic Compounds. *Phytochemistry* **2011,** *72* (2–3), 248–254.

Al-Ghanayem, A. A.; Al Sobeai, S. M.; Alhussaini, A. S.; Joseph, B.; Saadabi, A. M. Antifungal Activity of *Anastatica hierochuntica* L. Extracts Against Different Groups of Fungal Pathogens: An In-Vitro Test. *Rom. Biotechnol. Lett*. **2018,** *23* (6), 14135–14139.

Al Sobeai, S. M. In Vitro Cytotoxxicity and Antibacterial Evaluation of Aqueous, Methanolic and Ethanolic Extracts of *Anastatica hierochuntica* Against Pathogenic Bacteria. *Int. J. Curr. Res. Biosc. Plant Biol*. **2016,** *3* (6), 14–22.

Batanouny, K. H. *Wild Medicinal Plants in Egypt*; The Palm Press: Cairo, 1999; p 207.

Daoowd, W. S. In Vitro Antifungal Activity of Extracts of *Anastatica hierochuntica*. *Kufa J. Vet. Med. Sci.* **2013,** *4* (1), 142–148.

Daur, I. Chemical Properties of the Medicinal Herb Kaff Maryam (*Anastatica hierochuntica* L.) and Its Relation to Folk Medicine Use. *Afr. J. Microbiol. Res.* **2012,** *6* (23), 5048–5051.

El Ghazali, G. E.; Al-Khalifa, K. S.; Saleem, G. A.; Abdallah, E. M. Traditional Medicinal Plants Indigenous to Al-Rass Province. *Saudi Arabia. J. Med. Plants Res*. **2010,** *4* (24), 2680–2683.

El-Sayed, M.; El-Sherif, F.; Elhassaneen, Y.; El-Rahman, A. A. Potential Therapeutic Effects of Some Egyptian Plant Parts on Hepatic Toxicity Induced by Carbon Tetrachloride in Rats. *Life Sci. J*. **2012,** *9* (4), 3747–3755.

Eman, A. S.; Tailang, M.; Benyounes, S.; Gauthaman, K. Antimalarial and Hepatoprotective Effects of Entire Plants of *Anastatica hierochuntica*. *Int. J. Res. Phytochem. Pharmacol.* **2011,** 1, 24–27.

Farid, C. G.; Law. K. S. The True Rose of Jericho (*Anastatica heirochuntica* L.): Ultra-Structural Finding and Suggestion of Its Medicinal Properties. *Malays. J. Microscope*. **2009,** *5* (1), 19–26.

Friedman, J.; Stein, Z. The Influence of Seed-Dispersal Mechanisms on the Dispersion of *Anastatica hierochuntica* (Cruciferae) in the Negev Desert. *Israel J. Ecology*. **1980,** 43–50.

Hajjar, D.; Kremb, S; SIoud, S.; Emwas, A. H.; Voolstra, C. R.; Ravasi, T. Anti-Cancer Agents in Saudi Arabian Herbals Revealed by Automated High-Content Imaging. *PLoS ONE*. **2017,** *12*, e0177316.

Hansen, M. *Pathophysiology: Foundations of Diseases and Clinical Intervention*; W. B. Saunders Company: Philadelphia, U.S.A., 1998; pp 851–852.

Hashim, N. E.; Mohamed, Z. Biological Activities of *Anastatica hierochuntica* L.: A Systematic Review. *Biomed. Pharmacother.* **2017,** *91*, 611–620.

Havsteen, B. H. The Biochemistry and Medical Significance of the Flavonoids. *Pharmacol. Ther*. **2002,** *96* (2), 67–202.

Jacob, F.; Zipporah, S. The Influence of Seed Dispersal Mechanisms on the Dispersion of *Anastatica hierochuntica* (Cruciferae) in the Negev Desert, Israel. *J. Ecology* **1980,** *68* (1), 43–50.

Jaradat, N. Ethnopharmacological Survey of Natural Products in Palestine. *An-Najah Univ. J. Res*. **2005,** *19*, 13–67.

Karadaş, C.; Kara, D. Chemometric Approach to Evaluate Trace Metal Concentrations in Some Spices and Herbs. *Food Chem*. **2012,** *130*, 196–202.

Khalifa, T. I. M. A. A Pharmacognostical Study of Certain Species of *Anastatica*; Ph.D Thesis, University of Cairo, Egypt, 1980.

Knight, S., Devotion, Popular Belief and Sympathetic Magic Among Renaissance Italian Women: the Rose of Jericho as Birthing Aid. *Stud. Church Hist*. **2010,** *46*, 134–143.

Law, K. S.; Soon, L. K.; Mohsin, S. S. S.; Farid, C. G. Ultrastructural Findings of *Anastatica hierochuntica* L., (Sanggul Fatimah) Towards Explaining Its Medicinal Properties. *Ann. Microsc*. **2009,** *9*, 50–56.

Marzouk, M. M.; Abdel-Salam, M.; Al-Nowaihi.; Kawashty, S. A.; Saleh, N. A. M. Chemosystematic Studies on Certain Species of the Family Brassicaceae (Cruciferae) in Egypt. *Biochem. Systemat. Ecol.* **2010,** *38*, 680–685.

Mohamed, A. A.; Khalil, A. A.; El-Beltagi, H. E. S. Antioxidant and Antimicrobial Properties of Kaff Maryam (*Anastatica hierochuntica*) and Doum Palm (*Hyphaene thebaica*). *Grasas Y Aceites*. **2010,** *61* (1), 67–75. DOI: 10.3989/gya.064509.

Mossa, J. S.; Al-Yahya, M. A.; Al-Meshal, I. *Medicinal Plant of Saudi Arabia*; King Saud University: Riyadh, 1987.

Nakashima, S. H.; Matsuda, Y.; Oda, S.; Nakamura, F. M.; Xu, M.; Yoshikawa, Melanogenesis inhibitors from the desert plant *Anastatica hierochuntica* in B16 melanoma cells. *Bioorgan Med. Chem.* **2010,** 18 (6), 2337–2345.

Nani, D. Pengaruh air rendaman Rumput Fatimah (*Anastatica hierochuntica* L.) terhadap frekuensi kontraksi uterus tikus galur sprague dawley pada fase estrus. *J. Keperawatan Soedirman*. **2009,** *4* (1), 1–8.

Nani, D. Perubahan amplitudo kontraksi otot uterus tikus akibat pemberian Rumput Fatimah (*Anastatica hierochuntica* L.). *Mandala Health* **2010,** *4* (1), 47–52.

Nasir, E.; Ali, S. I. *Flora of Pakistan*; University of Karachi: Islamabad, Pakistan, 1980; pp 1010–4100.

Qnais, E.; Modallal, N.; Bseiso, Y.; Wedyan, M.; Alkhateeb, H. Evalution of the Antinociceptive Effects of the Essential Oil from Aerial Parts of *Anastatica hierochuntica* in Experimental Models. *Pharmacol. Online*. **2017,** *3*, 112–122.

Rahmy, T. R.; El-Ridi, M. R. Action of *Anastatica hierochuntica* Plant Extract on Islets of Langerhans in Normal and Diabetic Rats. *Egypt. J. Biol.* **2002,** *4*, 87–94.

Rameshbabu, S.; Messaoudi, A.; Alehaideb, Z. I., ALi, M. S.; Venktraman, A.; Alajmi, H.; Al-Eidi, H.; Matou-Nasri, S. *Anastatica hierochuntica* (L.) Methanolic and Aqueous Extracts Exert Antiproliferative Effects Through the Induction of Apoptosis in MCF-7 Breast Cancer Cells. *Saudi Pharm. J.* **2020,** S1319-0164(20)30146-8

Rasheed, R. A.; Bashir, A. K.; Ali, B. H. Fetal Toxicity of *Anastatica hierochuntica* L. in Mice. *FASEB J.* **1997,** *11* (3), 2413–2413.

Rizk, A. M.; Hammouda, F. M.; Ismail, S. I.; Hassan, N. M.; Ahmed, F. A. Constituents of Plants Growing in Qatar XX. Phytochemical Investigation of *Anastatica hierochuntica*: Note. *Int. J. Pharmacogn.* **2008,** *31*, 327–329.

Rizk, A. M., Williamson, E. M.; Evans, F. J. Constituents of Plants Growing in Qatar VII an Examination of Certain Plants for Anti-Inflammatory Activity. *Pharm. Biol.* **1985,** *23* (1), 1–4.

Salah, S.; Abdou, H. S.; El-Azeem, A. S. A. B. D.; Abdel-Rahim, E. A. The Antioxidative Effects of Some Medicinal Plants as Hypoglycemic Agents on Chromosomal Aberration and Abnormal Nucleic Acids Metabolism Produced by Diabetes Stress in Male Adult Albino Rats. *J. Diabetes Mellit*. **2011,** *1* (1), 6–14. DOI: 10.4236/jdm.2011.11002.

Sennoune, S.; Gerbi, A.; Duran, M. J.; Benkoel, L.; Pierre, S.; Lambert, R.; et al. A Quantitative Immunocytochemical Study of Na+, K+ATPase in Rat Hepatocytes After STZ-Induced Diabetes and Determination of Blood Glucose Using an Oxidase-Peroxidase System: A Non Carcinogenic Chromagen. *Am. Clin. Biochem.* **1999,** *6*, 24–30.

Shaban, F.; Al-Azzawie, H. F.; Mohammed, A. S. Effect of Alcoholic *Anastatica hierochuntica* Extract on some Biochemical and Histological Parameters in Alloxan Induced Diabetic Rats. *Iraqi J. Sci.* **2011,** *52* (4), 445–455.

Shah, A. H.; Bhandari, M. P.; N. O.; Al-Harbi, R. M.; Al-Ashban. Kaff-E-Maryam (*Anastatica hierochuntica* L.): Evaluation of Gastro-Protective Activity and Toxicity in Different Experimental Models. *Biol. Med*. **2014,** *6* (197), 1–10.

Sobhy, E. A.; Tailang, M.; Benyounes, S.; Gauthaman, K. Antimalarial and Hepatoprotective Effects of Entire Plants of *Anastatic hierochuntica*. *Int. J. Res. Phytochem. Pharmacol*. **2011,** *1* (1), 24–27.

Sooi, L. K.; Keng, S. L. Herbal Medicines: Malaysian Women's Knowledge and Practice. *Evid. Based Compl. Alt. Med.* **2013,** 1–10.

Soong, Y. Y.; Barlow, P. J. Antioxidant Activity and Phenolic Content of Selected Fruit Seeds. *Food Chem*. **2004,** *88* (3), 411–417.

Tayel, A. A.; El-Tras, W. F. Possibility of Fighting Food Borne Bacterial by Egyptian Folk Medicinal Herbs and Spices Extracts. *Egypt Public Health Assoc*. **2009,** *84* (1–2), 21–32.

Van Oudtshoom, R. K.; Van Rooyen, M. W. *Dispersal Biology of Desert Plants*; Springer-Verlag: Berlin, Germany; 1999.

Yoshikawa, M.; Morikawa, T.; Xu, F.; Ando, S.; Matsuda, H. (7R 8S) and (7S, 8R) 8-50 Linked Neolignans from Egyptian Herbal Medicine *Anastatica hierochuntica* and Inhibitory Activities of Lignans on Nitric Oxide Production. *Heterocycles* **2003b,** *60*, 1787–1792.

Yoshikawa, M.; Xu, F.; Morikawa, T.; Ninomiya, K.; Matsuda, H. Anastatins A and b New Skeletal Flavonoids with Hepatoprotective Activities from the Desert Plant *Anastatica hierochuntica*. *Bioorg. Med. Chem. Lett*. **2003a,** *13* (6), 1045–1049.

Zin, S. R.; Kassim, N. M.; Alshawsh, M. A.; Hashim, N. E.; Mohamed, Z. Biological Activities of *Anastatica hierochuntica* L: A Systematic Review. *Biomed. Pharmacother.* **2017,** *91*, 611–620.

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CHAPTER 6

Naphthalene—Isoquinoline Group of Alkaloid from Monotypic Family Ancistrocladaceae

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ABSTRACT

Ancistrocladus, a genus of monotypic family Ancistrocladaceae, comprises of ~25 species distributed in tropical Asia, Malaysia and West Africa. The genus is considered important due to its spending antimalarial, anti-HIV, antileishmanial, and a wide array of bioactivities. Most of the activities are attributed to a novel class of alkaloids categorised as naphthalene- isoquinoline. The current chapter is a comprehensive compilation of the family Ancistrocladaceae with respect to its distribution, bioactives and pharmacology. It can be inferred that more studies on bioactives from the family will help understand its extended use in pharmaceutical industries.

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6.1 INTRODUCTION

Ancistrocladus, a genus of monotypic family Ancistrocladaceae, comprises ~25 species distributed in Tropical Asia, Malaysia, and West Africa. The family consists of a single genus, *Ancistrocladus*, and about 25 species of lianas, found in the tropics of the old world (Table 6.1).

TABLE 6.1 Distribution of *Ancistrocladus* Species.

Sr. no.	Species	Distribution
1.	*Ancistrocladus abbreviatus*	Ivory Coast (Africa)
2.	*Ancistrocladus attenuatus*	Burma (Asia)
3.	*Ancistrocladus barteri*	Ivory Coast (Africa)
4.	*Ancistrocladus benomensis*	Malaysia (Asia)
5.	*Ancistrocladus carallioides*	Thailand (Asia)
6.	*Ancistrocladus cochinchinensis*	Vietnam (Asia)
7.	*Ancistrocladus congolensis*	Congo (Africa)
8.	*Ancistrocladus ealaensis*	Congo (Africa)
9.	*Ancistrocladus extensus*	Burma (Asia)
10.	*Ancistrocladus griffithii*	Thailand (Asia)
11.	*Ancistrocladus guineensis*	Nigeria (Africa)
12.	*Ancistrocladus hainanensis*	China (Asia)
13.	*Ancistrocladus hamatus*	Sri Lanka (Asia)
14.	*Ancistrocladus harmandii*	Laos (Asia)
15.	*Ancistrocladus heyneanus*	India (Asia)
16.	*Ancistrocladus korupensis*	Cameroon (Africa)
17.	*Ancistrocladu sletestui*	Congo (Africa)
18.	*Ancistrocladus likoko*	Congo (Africa)
19.	*Ancistrocladus pachyrrhachis*	Liberia (Africa)
20.	*Ancistrocladus robertsoniorum*	Kenya (Asia)
21.	*Ancistrocladus stelligerus*	Burma (Asia)
22.	*Ancistrocladus tanzaniensis*	Tanzania (Africa)
23.	*Ancistrocladus tectorius*	China, Laos, Malaysia, Thailand (Asia)
24.	*Ancistrocladus uncinatus*	Nigeria (Africa)
25.	*Ancistrocladus wallichii*	Sri Lanka (Asia)

A. heyneanus Wall. ex Grah. is a scandent shrub, with hooked branches, leaves are deep green, oblanceolate-oblong, subacute, glabrous, shining, and narrowed at base. Flowers are small, caducous, calyx lobes enlarged

into fruits, obovate, cuneate, with prominently reticulate veins. The genus is endangered and endemic to the Western Ghats of India distributed in Konkan: Matheran, Pen, Thana, Khandala, Parghat, Ramghat, and Kanara, and in evergreen forests of North Kanara.

Ramamoorthy (1976) suggested that *A. heynenaus* may be the taxonomic synonym of *A. hamatus* and the same with reference to Ramamoorthy's publication has been mentioned by Gereau (1997). This may be probably because of the similarities in the habit of both the plants and its distribution. *Ancistrocladus heyenanus* is endemic to the Western Ghats of India, whereas *A. hamatus* is found in Sri Lanka. The Western Ghats of India and Sri Lanka is time and again considered as a single component for the reason that they share biogeographical history (Gunawardene et al., 2007). Thus, the suggestion made by Ramamoorthy should not be sidelined and should be restudied for the possible merging of the two.

Previous reports indicated the curative potential of crude extract of roots, leaves, and stems of *Ancistrocladus* spp. in various ailments, such as dysentery, fever, diarrhea, malaria, etc. (Ruangrungsi et al., 1985; Bringmann et al., 1990). In Thailand, young leaves are used as food juice flavor (Burkill, 1966; Usher, 1974).

Few of the other related studies present the optimization of extraction techniques for the quantification of betulinic acid in *A. heyneanus* (Pai et al., 2011).

6.2 BIOACTIVES

The genus is a source of a novel group of alkaloids known as naphthalene-isoquinolines (Govindachari and Parthasarathy, 1977; Cordell, 1981). Michellamines A, B (Manfredi, 1991), and D–F (Hallock et al., 1997), a group of dimeric napthylisoquinoline alkaloid has shown to have promising anti-human immunodeficiency virus (HIV) activity. These michellamines have been reported from other species of *Ancistrocladus*; however, there were no reports of michellamines confirming from *A. heynenaus*. Hallock et al. (1994, 1997) reported new "monomeric" alkaloids, korupensamines A–E, and the related N–methyltetrahydroisoquinoine. Napthylisoquinoline alkaloids can be divided into subtypes according to the linkage between their napthyl and isoquioline moieties. Some of these alkaloids have antifungal, antimalarial, or antiviral activity (Bringmann et al., 1992; Francois et al., 1994, 1996; Boyd et al., 1994). Bringmann et al. (2003) described the isolation and structural elucidation of a bioactive alkaloid ancistrolikokine D,

ancistroealanine A, and napthoic acid derivatives. Bringmann and co-workers (1998) reported polyketide folding mode in isoshinanolone and plumbagin biosynthesis from *A. heynenaus*.

The napthylisoquinoline alkaloids constitute structurally, biosynthetically, and pharmacologically useful biaryls. About 120 alkaloids belonging to this category have been isolated so far and all of them from the family Ancistrocladaceae and Dionocophyllaceae, serving them as phytochemical markers.

A. heyneanus is indigenous to India (Bringmann et al., 2004; Govindachari, 2002). It is a tropical liana distributed in the Western Ghats of India. Following are the different metabolites studied in *A. heyneanus* (Table 6.2).

TABLE 6.2 Metabolites Produced in Different Parts of *A. heyneanus* and Methods Used in Their Detection and Structural Elucidation.

Metabolite	Coupling[a]	Plant parts	References	Method used[b]
Ancistrocladine	5,1′	Root	Govindachari and Parthasarathy (1970)	NMR, IR, MS, FT-Raman
Ancistrocladisine	C-7 and C-1′	Root	Govindachari et al. (1972)	NMR, IR, MS, FT-Raman
Ancistrocladidine	7,3′	Root	Govindachari et al. (1973)	NMR, GC-MSD, IR, CD, FT-Raman
Ancistroheynine A	C-7 and C-8′	Shoot	Bringmann et al. (1996)	HPLC, IR, GC, NMR, FT-Raman
Betulinic acid	–	Aerial parts	Bringmann et al. (1997)	NMR, IR, MS
Ancisheynine	C-8′ and N-2	Shoot	Yang et al. (2003)	NMR, ROESY
Ancistrocladidine	7,3′	Leaves	Bringmann et al. (2004)	NMR, GC-MSD, IR, CD
Ancistrotanzanine C	7,3′	Leaves	Bringamann et al. (2004)	NMR, GC-MSD, IR, CD
Ancistroheynine B	7,3′	Leaves	Bringamann et al. (2004)	NMR, GC-MSD, IR, CD

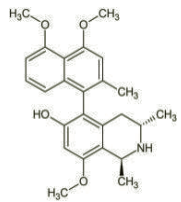
[a]Coupling of naphthalene with isoquinoline.

[b]Methods used by different workers for detection and structural elucidation of metabolites.

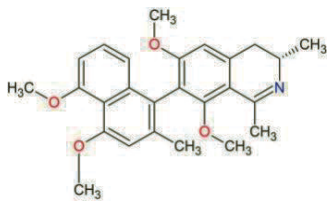
6.3 PHARMACOLOGY

6.3.1 ANTIVIRAL ACTIVITY

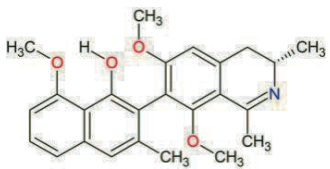
A. heyneanus plant extracts were active on Herpes simplex Virus Type 1 at 50 µg/mL (Silva et al., 1997). Betulinic acid from the plant is reported



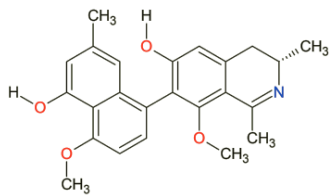
Ancistrocladine



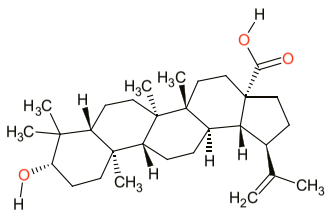
Ancistrocladisine



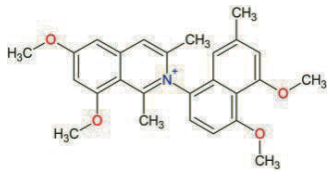
Ancistrocladidine



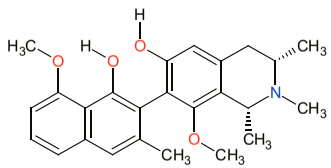
Ancistroheynine A



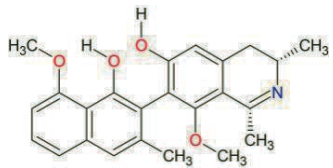
Betulinic Acid



Ancisheynine



Ancistrotanzanine C



Ancistroheynine B

FIGURE 6.1 Compounds from *Ancistrocladus heyneanus.*

to inhibit HIV (Bringmann et al., 1997; Singh et al., 2005). In the 1990s, a new dimension toward pharmacological activity of this small family arose by the identification of michellamines from *A. korupensis* (Boyd et al., 1994). These were the first dimericnaphthylisoquinolines (NIQ) with strong anticytopathic activities against the HIV. However, author has not found any direct reference of the presence of michellamine in *A. heyneanus*.

6.3.2 ANTIBACTERIAL ACTIVITY

Aswathanarayan and Rai (2013) reported marked antibacterial activity against food-related bacteria *Escherichia coli* and *Salmonella typhi* of *A. heyneanus* and *Rotula aquatica*. Crude extracts as well as isolated alkaloid fractions of *A. heyneanus* showed considerable activity against Gram-positive bacteria but not against Gram-negative bacteria (More et al., 2012).

6.3.3 ANTIOXIDANT EFFICACY

Antioxidant efficacy of *A. heyneanus* along with *R. aquatica* was reported by Aswathanarayan and Rai (2013). They reported significant antioxidant activity determined by total antioxidant capacity, ABTS, DPPH free radical scavenging activities, inhibitory activity toward β-carotene bleaching, lipid peroxidation, and DNA protection activity.

6.3.4 ANTIMALARIAL ACTIVITY

Antiplasmodial activity of extracts of *A. abbreviatus*, *A. barteri, Triphyophyllum peltatum* (Francois et al., 1994, 1995), *A. barteri*, *A. heyneanus, A. robertsoniorum*, *A. tectorius,* and *T. peltatum* (Francois et al., 1997) has displayed considerable activity against *Plasmodium falciparum* and *P. berghei*, accentuating its potential antimalarial value. Betulinic acid has been reported to exhibit a wide array of biological properties. Bringmann et al. (1997) reported moderate antiplasmodial in vitro activity with IC_{50} value 10.46 pg/ml of betulinic acid against malaria. Also, in a separate study by François et al. (1997) similar in vitro activity against *P. falciparum* has been demonstrated. Similar activity has also been demonstrated in various new compounds identified under NIQ, namley, Ancisheynine A, ancistroheynine A, B, ancistrocladidine, ancistrotanzanine from *A. heyneanus* (Bringmann

et al., 1996; Yang et al., 2003; Bringmann et al., 2004) suggesting the plant to be a source of antimalarial and antiviral compounds. *Ancistrocladus robertsoniorum,* an East African liana, was reported with four new naphthyl-isoquinoline alkaloids ancistrobertsonines B, C ancistrobertsonine D, and its 1,2-didehydro analog possessing moderate antimalarial activity (Bringmann et al., 1999).

6.3.5 ANTITRYPANOSOMAL AND ANTILEISHMANIAL ACTIVITIES

The plant has also been studied for antitrypanosomal and antileishmanial activities (Bringmann et al., 2004). Apart from the above, a Chinese species *A. tectorius* is also reported to have such activity due to their phytocompounds, namely, ancistectorine A1, N-methylancistectorine A1, ancistectorine A2, 5-epi-ancistectorine A2, ancistectorine A3, ancistectorine B1, and ancistectorine C1 (Bringmann et al., 2012). Similar reports of chemical compounds from the same group have been reported in *Ancistrocladus congolensis*, against protozoan parasites causing severe tropical diseases (Bringmann et al., 2008). Scotti et al. (2016) reviewed natural products for antileishmanial and antitrypanosomal activity, it includes plants from the family Menispermaceae, Celastraceae, Malvaceae, Euphorbiaceae, Rubiaceae, Papaveraceae, Apocynaceae, Ancistrocladaceae, Rutaceae, Annonaceae, and Amaryllidaceae. In a separate review, Veigaco workers (2020) enlisted several species along with *Ancistrocladus* species as antileishmanial potential alkaloids.

6.3.6 ANTICANCER ACTIVITY

Betulinic acid, a naturally occurring pentacyclictriterpene, has also been reported to show potential antitumor effects. Kuo et al. (2009) also reported a group of terrestrial plants possessing such activity, and *A. heyneanus* was among them. Antitumoral activity of *A. tectorius* is reported by Bringmann and co-workers (2013).

6.4 CONCLUSION

A. heyneanus is the only member of the family Ancistrocladaceae available in the Indian subcontinent. Identification issues with Sri Lankan species *A. hamatus* needs more studies and clarification. The plant is a source of

novel napthylisoquinolinealkaloids. Pharmacologically, the plant has been widely explored for its anti-HIV, antimalarial, antitrypanozomal, and anti-leishmanial properties. Antioxidant and antimicrobial activities are few others to be named that are explored very recently. Due to its wide array of phytocompounds, it will be interesting to study more biological activities. Antifungal, hepatoprotective, antidiabetic, and cardioprotective are some of the other activities that need to be studied and reported.

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KEYWORDS

- **napthalene-isoquinoline**
- **alkaloids**
- **Ancistrocladaceae**
- **bioactives**
- **pharmacology**

REFERENCES

Aswathanarayan, J. B.; Rai, R. V. In Vitro Evaluation of Antioxidant and Antibacterial Activities of *Rotula aquatica* and *Ancistrocladus heyneanus*: Antioxidant and Antimicrobial Activity of Medicinal Plants. *J. Pharm. Res.* **2013,** *6* (2), 313–317.

Boyd, M. R.; Hallock, Y. F.; Cardellina, J. H. II; Manfredi, K. P.; Blunt, J. W.; McMahon, J. B.; Buckheit, R. W.Jr.; Bringmann, G.; Schaffer, M.; Gragg, G. M.; Thomas, D. W.; Jato, J. G. Anti-HIV Michellamines from *Ancistrocladus korupensis*. *J. Med. Chem.***1994,** *37*, 1740–1745.

Bringmann, G.; AkeAssi, L.; Rubenacker, M.; Ammermann, E.; Lorenz G. D. O. S. DE Appl. 4117080 A1, 1991; European Patent Application EP 0515 856 A1, 1992.

Bringmann, G.; Dreyer, M.; Michel, M.; Tayman, F. S. K.; Brun, R. Ancistroheynine B and Two Further 7,30-Coupled Naphthylisoquinoline Alkaloids from *Ancistrocladus heyneanus* Wall. *Phytochem* **2004,** *65*, 2903–2907.

Bringmann, G.; Koppler, T. D.; Wiesen, B.; Francois, G.; Sankara Narayanan, A. S.; Almeida, M. R.; Schneider, H.; Zimmermann, U. Ancistroheynine A, the first 7,8′-Coupled

Naphthylisoquinoline Alkaloids from *Ancistrocladus heyneanus*. *Phytochemistry* **1996,** *43*, 1405–1410.

Bringmann, G.; Pokorny, F.;Reuscher, H.; Lisch, D.; Assi, L. Novel Ancistrocladaceae and Dioncophyllaceae Type Naphthyliosquinoline Alkaloids from *Ancistrocladus abbreviatus*: A Phylogenetic Link Between the Two Families? *Planta Med.* **1990,** *56*, 496–497.

Bringmann, G.; Saeb, W.; Rückert, M.; Mies, J.; Michel M.; Mudogo V.; Brun R. Ancistrolikokine D, a 5,8′-Coupled Naphthylisoquinoline Alkaloid, and Related Natural Products from *Ancistrocladus likoko*. *Phytochemistry* **2003,** *62*, 631–636.

Bringmann, G.; Teltschik, F.; Michel, M.; Busemann, S.; Ruckert, M.; Haller, R.; Bars Robertson, S. A.; Kaminsky, R. Ancistrobertsonines B, C, and D as well as 1, 2—Didehydroancistrobertsonine D from *Ancistrocladus robertsoniorum*. *Phytochemistry* **1999,** *52*, 321–332.

Bringmann, G.; Zhang, G.; Ölschläger, T.; Stich, A.; Wud, J.;Chatterjee, M.; Brun, R. Highly Selective Antiplasmodial Naphthylisoquinoline Alkaloids from *Ancistrocladus tectorius*. *Phytochemistry* **2013,** *91*, 220−228.

Bringmann G.; Spuziak J.; Faber, J. S.; Gulder, T.; Kajahn, I.; Dreyer, M.; Heubl, G.; Brun, R.; Mudogo V. Six Naphthylisoquinoline Alkaloids and a Related Benzopyranone from a Congolese *Ancistrocladus* Species Related to *Ancistrocladus congolensis. Phytochemistry* **2008,** *69* (4), 1065–1075.

Bringmann, G.; Saeb, W.; Assi, L.; Francois, G.; Sankara Narayanan, A. S.; Peters, K.; Peters, E. M. Betulinic Acid: Isolation from *Triphyophyllum peltatum* and *Ancistrocladus heyneanus*, Antimalarial Activity, and Crystal Structure of the Benzyl Ester. *Planta Med.* **1997,** *63*, 255–257.

Bringmann, G.; Wohlfarth, M.; Rischer, H.; Rückert, M.; Schlauer, J. The Polyketide Folding Mode in the Biogenesis of Isoshinanolone and Plumbagin in *Ancistrocladus heyneanus* (Ancistrocladaceae).*Tetrahedron Lett.***1998,** *39*, 8445–8448.

Burkill I. H. *A Dictionary of the Economic Products of the Malay Peninsula*; Crown Agents: London; 1966.

Cordell G. A. *Introduction to Alkaloids—A Biogenetic Approach*. Wiley-Interscience:New York, 1981; p 219.

Francois, G.; Bringmann, G.; Dochez, C.; Schneider, C.; Timperman, G.; AkéAssi, L. Activities of Extracts and Naphthylisoquinoline Alkaloids from *Triphyophyllum peltatum*, *Ancistrocladus abbreviatus* and *Ancistrocladus barteri* Against *Plasmodium berghei* (Anka strain) In Vitro. *J. Ethnopharmacol*. **1995,** *46*, 115–120.

Francois, G.; Bringmann, G.; Phillipson, J. D.; AkéAssi, L.; Dochez, C.; Rübenacker, M.; Schneider, C.; Wéry, M.; Warhurst, D. C.; Kirby, G. C. Activity of Extracts and Naphthylisoquinoline Alkaloids from *Triphyophyllum peltatum*, *Ancistrocladus abbreviatus* and *A. barteri* Against *Plasmodium falciparum* In Vitro. *Phytochemistry* **1994,** *35*, 1461–1464.

Francois, G.; Timperman, G.; Haller, R. D.; Bär, S.; Isahakia, M. A.; Robertson, S. A.; Zhao, C.; De Souza,N. J.; AkéAssi, L.; Holenz, J.; Bringmann, G. Growth Inhibition of Asexual Erythrocytic Forms of *Plasmodium falciparum* and *P. berghei* In Vitro by Naphthylisoquinoline Alkaloid—Containing Extracts of *Ancistrocladus* and *Triphyophyllum* Species. *Int. J. Pharmacogn*. **1997,** *35* (1), 55–59.

Francois, G.;Timperman, G.; Holenz, J.; Ake´Assi, L.; Geuder, T.; Maes, L.; Dubois, J.; Hanocq, M.; Bringmann, G. Naphthylisoquinoline Alkaloids Exhibit Strong Growth-Inhibiting