Mubashir Hussain Masoodi
Muneeb U Rehman *Editors*

Edible Plants in Health and Diseases

Volume II : Phytochemical and Pharmacological Properties

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Contents

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Zingiber officinale: Its Ethanobotanical Uses, Phytochemistry, and Pharmacology

1

Pradeep Singh, Garima Mishra, Faheem Hyder Pottoo, Bhuvnesh Singh, and Mulugeta Molla Zeleke

Abstract

Zingiber officinale Roscoe is a well-recognized herbal plant throughout the world. Ginger is not only consumed as dietary spice but has also been employed in the traditional medicinal systems as herbal remedy since antiquity. Ginger offers health benefits mainly attributable to many bioactive phytochemicals including phenolic compounds, terpenes, flavonoids, carbohydrates, proteins, minerals, and many more. The principle phenolic compounds in ginger that lead to a plethora of biological activities are gingerols, shogaols, and paradols. Rhizome is an essential nutritional and medicinal component of ginger. The volatile components impart characteristic aroma or fragrance to ginger. This spice is traditionally used to relieve pain, constipation, digestive troubles, fever, cramps, inflammation, hypertension, dementia, and infections. Accumulated evidences have illustrated that ginger and its derivatives exhibit multiple pharmacological effects including antioxidant, anti-inflammatory, antidiabetic, antiemetic, anti-obesity, antimicrobial, anticancer, cardioprotective, and neuroprotective. Ginger thus can be used as potent and innovative therapeutic alternative for the prevention and management of acute and chronic disorders. This chapter highlights current knowledge about the ethanobotanical uses, phytochemicals, and biological activities of ginger and suggests that this updated

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information will be fruitful for researchers to investigate novel and unexplored applications.

Keywords

Adrack · Ginger · Gingerol · Oleoresin · Paradols · Phenylpropanoids · Sonth · *Zingiber officinale* · *Zingiber zingiber*

Abbreviations

ABTS	2,2′-Azinobis-(3-ethylbenzthiazolinesulfonic acid)
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase or aspartate aminotransferase
BHA	Butylated hydroxyl aniline
BHT	Butylated hydroxyl toluene
BSA	Bovine serum albumin
CAA	Cellular antioxidant activity
Cdk	Cyclin-dependent kinase
cIAP	Cytosolic inhibitor of apoptosis
CINV	Chemotherapy-induced nausea and vomiting
COX	Cyclooxygenase
DOCA	Deoxycorticosterone acetate
DPPH	2,2-Diphenyl-1-picryl-hydrazyl
FRAP	Ferric reducing antioxidant power
GDNPs	Nanoparticles derived from edible ginger
GEO	Ginger essential oil
GSH	Glutathione
HMGCoA	3-Hydroxy-3-methyl-glutaryl-coenzyme A
HTN	Hypertension
IL	Interleukin
LOX	Lipooxygenase
MBC	Minimum bactericidal concentration
MIC	Minimum inhibitory concentration
NF-kB	Nuclear factor kappa B
Nrf2	Nuclear factor erythroid 2-related factor 2
NVP	Nausea and vomiting in pregnancy
ORAC	Oxygen radical absorbance capacity
OSI	Oil stability index
PGE2	Prostaglandin E_2
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor

1.1 Introduction

Nature has provided us a precious gift in the form of food, dietary supplements, as well as drugs which are beneficial for the well-being (Balentine et al. 1999). In present time, people have strong belief in natural products obtained from various sources including plants, animals, marine, microorganisms, etc. It is thought that the drugs derived from natural sources are effective, safe, and nontoxic (Singh et al. 2016). India is a major hub for medicinal plants that make a significant contribution to the health system. These medicinal plants have great therapeutic value in the treatment of several diseases. It has been documented that medicinal plant constitutes more than 90% of traditional medicine recipes/remedies (Sofowora et al. 2013).

Medicinal plants belonging to the family Zingiberaceae are ubiquitously found throughout the tropics and have great significant value across the globe. Of these, gingers are well-recognized natural resources providing a number of beneficial products including food, spices, medicines, perfumes, etc. The ginger family represents around 53 genera as well as over 1200 species across the world, while India has 20 genera and over 200 species (Kumar et al. 2013).

Zingiber officinale, popularly known as adarakah in Hindi, has been largely consumed as spice and medicine in folk and traditional medicine systems since long. The plant is indigenous to Southeast Asia and also distributed in Europe (Roufogalis 2014). India, China, Australia, Nigeria, as well as Jamaica are the highest ginger exporting countries. The plant is grown in different states of India including Kerala, Orissa, Karnataka, Arunachal Pradesh, West Bengal, Madhya Pradesh, and Sikkim. Kerala is considered as the biggest producer making about 30–40% of total production. Chochin and Calicut gingers are the two major varieties of Indian ginger (Kubra and Rao 2012). Besides its utility in food, ginger has broad-spectrum biological properties. It is employed as herbal medicine in various ailments such as pain, cough, vomiting, and gastric problems (Singh et al. 2016). It exhibits potent antioxidant, anti-inflammatory, antipyretic, cardiovascular, antimicrobial, anticancer, and other pharmacological properties (Bhandari and Sethiya 2018; Mashhadi et al. 2013). The health-promoting benefits of ginger can be credited to its phytochemicals. The principle constituents of ginger are volatile oils, terpenoids, and flavonoids (Baliga et al. 2013). In addition, ginger rhizomes are rich in carbohydrates, fatty oils, proteins, crude fiber, ash, and water (Mbaveng and Kuete 2017). Ginger is used as promising nutraceuticals and additives in food industry. In Ayurveda, it is popularly known as "The great Medicament" and is considered as safe herbal medicine (Tan and Vanitha 2004). The current chapter recapitulates the most salient report on ethnobotany, phytochemistry, and pharmacology of *Zingiber officinale*.

1.2 Origin and History

Ginger is a perennial plant with characteristic aroma and flavor. The major part used as spice and medicine includes the rhizome that is horizontally connected with the stem. Ginger was originally grown in Southeast Asia and largely cultivated in other countries for medicinal purpose (Blumenthal et al. 2000; Sekiwa et al. 2000). Its generic name zingiber comes from the Greek word "Zingiberis," originating from the Sanskrit term "Singabera." The scientific name *Zingiber officinale* was given by William Roscoe (the English botanist) in 1807. It is claimed that ginger was employed as root tonic for more than 5000 years in various illnesses in India and China. Furthermore, it was used as flavoring agent since ancient time. About 2000 years ago, the Roman Empire had given it medicinal value. Ginger remained a widely popular ingredient in Europe. Even after the collapse of the Roman Empire, Arab merchants have governed the trade in ginger and other spices for centuries (CABI 2020; Khodaie and Sadeghpoor 2015). It has been mentioned that in the ninth century, ginger was one of the most popular spice introduced in Europe, while in the thirteenth century, Arab people incorporated it into East Africa. Ginger in the tenth century was recognized as medicinal drug in England. The spice was further emerged in West Africa and other tropical regions by Portuguese in the sixteenth century. Marco Polo during his visit introduced ginger in China and Sumatra and transported it Europe also (Shahrajabian et al. 2019a, b).

1.3 Botanical Description

Zingiber officinale is an evergreen plant (Figs. 1.1 and 1.2) that grows around 1 m long. Stem is erect with aerial shoots and fibrous roots. Leaves are simple, alternate, lanceolate, narrow, and long having sheath at the base. Rhizomes are pale yellow, aromatic, and 7–15 cm long and 1–1.5 cm broad with thick lobed. They grow horizontally just beneath the soil surface. The flowers are bisexual and small; petals 3, lip shaped, and yellowish-orange; calyx three lobed and tubular; corolla bilabiate; stamens 3 forming a whorl; ovary inferior, syncarpous; and style filiform and stigma subglobose type. The inflorescence is spiked and irregular (Kirtikar and Basu 1993; Weidner and Sigwart 2000). Fruit is thin-walled capsule, red colored, and three-valved. Seeds are small, black, and arillate.

1.4 Taxonomy

Kingdom: Plantae
Division: Angiosperm
Class: Monocotyledons
Subclass: Zingiberidae
Order: Zingiberales
Family: Zingiberaceae

Fig. 1.1 Ginger plant with fresh rhizome

Fig. 1.2 Dried rhizome

Genus: *Zingiber*

Species: *officinale*

Synonyms: *Zingiber cholmondeleyi*, *Zingiber majus*, *Zingiber missionis*, *Curcumia longifolia*

1.5 Common Vernacular Names

See Table 1.1.

1.6 Traditional Uses

Ginger has been well documented as folk medicine. This plant is a key element of several herbal medicines. Ginger plays a promising role in Ayurvedic, Siddha, Chinese, Arabic, and African folk medicines (Singh and Singh 2019). People from different origin and culture use ginger as herbal remedy since time immemorial. The important traditional uses of ginger in different systems including Indian, Unani, Chinese, and Siddha have been described below (Semwal et al. 2015).

1.6.1 The Indian System of Medicine

Ginger's role in the Indian system of medicine has been extensively recorded. It is the main ingredient of food and traditional Indian drinks. Fresh and dry gingers are used in Ayurvedic system to cure cough, cold, fever, headache, fever, nausea,

Table 1.1 Common vernacular names of ginger (Abdulrahaman et al. 2015; Kumar et al. 2011)

Languages	Common vernacular name
Hindi	Adi, adrack, sonth
Sanskrit	Adraka, shunthi, shringaveran, nagara
English	Ginger
Urdu	Adrak
Punjabi	Adi, adrak
Gujarati	Adu
Bengali	Ada
Marathi	Adra, ale
Tamil	Allam, injee, inji, lakottai
Telgu	Allamu, allam
Malayalam	Inchi
Kannad	Alla, hasishunti
Oriya	Ada, adraka
Chinese	Shen jiang, chiang, jiang, sang keong, jeung
Nepali	Aduwa, sutho
Dutch	Gember
Spanish	Gengibre
French	Gengembre
German	Gemeiner ingber
Indonesian	Jahe, lia, jae, aliah
European	Gingembre (French), ingwar (German), zenzero (Italian), jengibre (Spanish)

muscular pain, acute and chronic respiratory diseases (asthma, bronchitis), inflammatory conditions, gastric troubles (indigestion, flatulence, and appetite), allergy, and intestinal illness. Apart from that ginger is used to treat piles, ascites, throat cleaning, eructation, and neck pain. Ginger has anti-inflammatory, anti-edematous, and antidiarrheal effects (Jayashree et al. 2015). In addition, ginger is an excellent memory enhancer. The outer thin covering of ginger can be recommended as carminative and also a good remedy for opacity of cornea (Nadkarni 1998). Furthermore, ginger is internally given as tonic in Cambodia and topically applied to cure boils. Fresh ginger mixed with honey and ghee is considered as good home remedy for the treatment of cough. The juice prepared from ginger is used as potent diuretic (Kirtikar and Basu 1991). In contrast to fresh ginger, dry ginger has been documented as antifilarial and antiarthritic agent. In addition, powdered ginger is used as a snuff. The paste of dry ginger with water is externally beneficial for eyelids, while the mixture of powdered dry ginger, rock salt, black pepper, and long pepper added with fresh ginger juice is used as gargle and an effective treatment for phlegmatic affections (Pruthy 1979).

1.6.2 The Chinese System of Medicine

Ginger rhizome has been extensively employed as medicine in the Chinese medicine system (Remadevi et al. 2004). The Chinese records have shown that ginger was used to relieve from various illnesses such as diarrhea, cholera, nausea, stomachache, toothaches, haemorrage, and rheumatism. Ginger makes about half of all herbal prescriptions in modern China in combination with other herbal medicines (Afzal et al. 2001; Shahrajabian et al. 2019a, b). Traditionally, ginger is a good remedy for dyspepsia and colic conditions (Grant and Lutz 2000; Keys 1985; Sharma 2017). Specifically, ginger is said to be spicy and hot as it keeps the body warm and employed in cold conditions and strengthen the body after blood loss (Mishra et al. 2012). In addition, ginger is a promising herbal medicine for cardiovascular diseases (Surh et al. 1998).

1.6.3 The Traditional Medicine of Iran

Ginger is considered as potent herbal therapy in Iranian traditional system of medicine. The drug is used as antiemetic, antioxidant, and anti-inflammatory agent. It is given in many other ailments including gastrointestinal troubles, respiratory diseases, nausea, migrane, depression, atherosclerosis, and gastric ulcers. Ginger lowers cholesterol level (Surh et al. 1998).

1.6.4 The Unani System of Medicine

Ginger in Unani medicine is used as aphrodisiac, digestive, carminative, and sedative. In addition, it is used to cure rheumatism, headaches, lumbago, and nervous disorders. Ginger is an effective anthelmintic drug (Nadkarni 1998). Ginger also has wide applications in veterinary field. It is applied as medicine in cattle and horses for treating rheumatism and atonic indigestion and as antispasmodic drug (Blumenthal 1999; Pakrashi and Pakrashi 2003).

1.6.5 Ginger in Siddha

Ginger is extensively used in Siddha for several diseases such as cough, diarrhea, pain, and nausea. Ginger in conjunction with other herbal drugs relieves from gastritis, loss of appetite, vomiting, indigestion, and pitha diseases (Semwal et al. 2015).

1.6.6 Other Medicinal Uses

Despite tremendous use of ginger in several traditional systems as mentioned in the above section, ginger rhizome and other plant parts have also been reported for the treatment of ailments. Crushed ginger rhizomes boiled with water and tea provide taste and flavor to tea which is used to reduce depression and lethargy in many states of India. The ginger powder added with other natural ingredients like clove, caraway, and cardamom has been employed to cure digestive problems. Indonesians use ginger to relieve from fatigue and indigestion. Ginger is believed to be taken by Philippians for the treatment of sore throat, while Japanese has been using ginger to improve blood circulation (Ashokkumar et al. 2020a, b). In Malaysia, pounded leaves of ginger plant are applied externally as poultice in headache, and leaves are directly eaten against rheumatism and stomach pain. Young shoots are also used in the treatment of rheumatism (CABI 2020). A mixture of ginger and palm tree juice was consumed to cure the flu in Burma (Semwal et al. 2015).

1.7 Phytochemistry of Ginger

Zingiber officinale is a promising candidate due to its nutritional and therapeutic values. Ginger has diverse range of phytochemicals which are essential for good health. Chemical investigations of ginger have reported more than 400 phytoconstituents including carbohydrates, proteins, amino acids, lipids, glycosides, flavonoids, saponins, phytosterols, dietary fibers, and terpenoids (Prasad and Tyagi 2015).

1.7.1 Nutrient Composition

Ginger is an essential part of dietary supplement and food products in daily life as it imparts flavor and nutrition to human beings. Both fresh and dried gingers are comprised of carbohydrates, proteins, fat fibers, ash, minerals, vitamins (B1, B2, B5, C), and lipids including fatty acids, lecithins, phosphatidic acid, and glycerides. Some other nutritionally important metabolites like carotenoids and flavonoids are also present in fresh ginger (Balogun et al. 2019; Ibrahim et al. 2010). However, fresh and dried gingers greatly differ in their nutrient composition depending on variety, drying, and storage conditions (Ashokkumar et al. 2020a, b; Shakya 2015). The nutrient composition of ginger is as listed in Table 1.2.

1.7.2 Chemical Composition of Ginger Essential Oils

Although the genus *Zingiber* has worldwide importance due to its medicinal and biological attributes, of all genera, *Zingeber officinale* is well-recognized and extensively studied plant for its pharmacological properties (Sharifi-Rad et al. 2017). As previously mentioned, ginger is rich in many chemical compounds like carbohydrates, proteins, aminoacids, etc. Apart from that there are two main classes of compounds, namely, volatile oil/essential oils and nonvolatile compounds. Nonvolatile compounds of ginger are also termed as phenolic compounds which are implicated in many pharmacological activities (Ashraf et al. 2017). The molecular structures of chief chemical constituents are as shown in Fig. 1.3.

1.7.3 Volatile Oil/Essential Oil Composition

Ginger essential oil (GEO) is pale yellow- to light amber-colored oil that primarily is responsible for distinct fragrance or aroma of ginger (Bellik 2014). The yield of ginger oil varies on a wet and dry basis depending on the type of variety used.

Table 1.2 Nutrient composition of ginger (Singh et al. 2017; Shahrajabian et al. 2019a; b)

S. no.	Name of nutrient	Examples of nutrient
1	Carbohydrates	Dietary fiber, sugar
2	Protein	–
3	Water	–
4	Phytosterols	–
5	Fats and fatty acids	Saturated fat, monounsaturated fat, polyunsaturated fat, omega-3 fatty acids, omega-6 fatty acids
6	Vitamins	Thiamin, riboflavin, niacin, vitamin B6, folic acid, ascorbic acid, vitamin K, vitamin E, pantothenic acid
7	Minerals	Sodium, potassium, magnesium, iron, calcium, zinc, copper, manganese, selenium

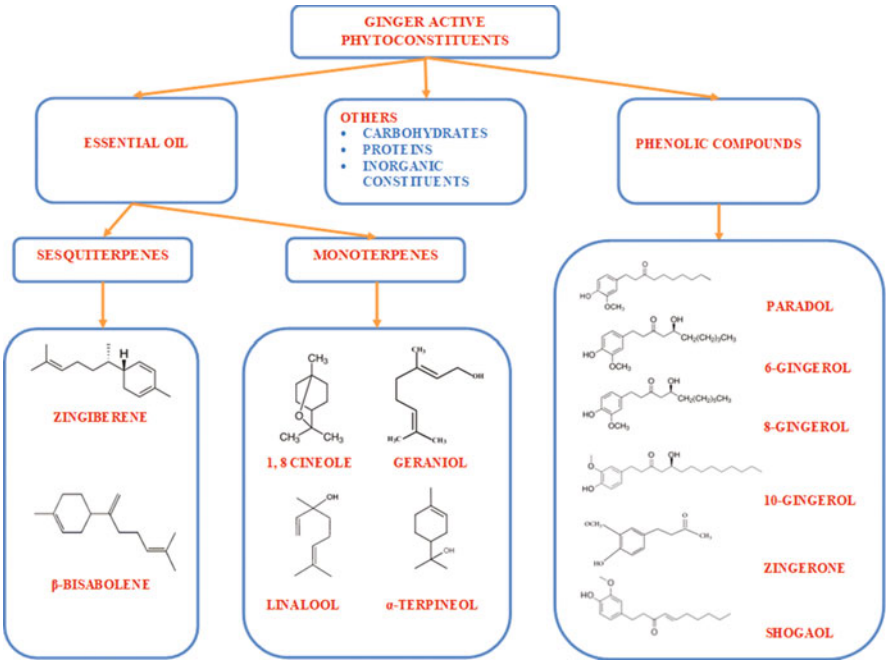

Fig. 1.3 Molecular structures of chief chemical constituents of ginger

Table 1.3 Percentage yield of GEO using different extraction methods

Rhizome	Extraction method	Yield (%)	Reference
Fresh	Hydro-distillation	0.20–1.79	Heritier et al. (2018)
	Super critical fluid extraction	0.24–2.62	Mesomo et al. (2013)
Dry	Hydro-distillation	1.10–4.17	Kiran et al. (2013) and Stoyanova et al. (2006)
	Steam distillation	2.1	Stoyanova et al. (2006)
	Ionic liquid-based microwave-assisted extraction	0.72	Guo et al. (2017)

Similarly, chemical composition of oil also gets affected from plant part, extraction methods, source of rhizomes, geographical conditions, and ginger cultivars (Mahboubi 2019). Table 1.3 illustrates the yield of GEO extracted from fresh and dry rhizomes using extraction method. The volatile fraction of ginger is rich in terpenes predominantly monoterpenes and sesquiterpenes. Monoterpenes are the most abundant components of fresh ginger. Sesquiterpenes are considered to add flavor to ginger (Butt and Sultan 2011; Dhanik et al. 2017). Zingiberene and β-bisaboline are the major sesquiterpene hydrocarbons that impart flavor to ginger. Likewise, α-curcumene, α-farnesene, and β-sesquiphellandrene are the other sesquiterpenes present in ginger (Nampoothiri et al. 2012; Wang et al. 2006).

GC-MS investigation of GEO extracted from rhizomes has shown the presence of relatively large amount of monoterpenoids designated as 1,8-cineole (10.9%), linalool (4.8%), borneol (5.6%), alpha-terpineol (3.6%), neral (8.1%), geraniol (14.5%), geranial (9.5%), trans-dimethoxy citral (5.0%), and geranyl acetate (6.3%). Five novel compounds such as trans-linalool oxide, trans-linalool oxide acetate, (Z)-dimethoxycitral, (E)-dimethoxy citral, and epi-zingiberenol were also identified (Gupta et al. 2011). Moreover, another study highlighted the identification of 37 compounds, of these, citral, isoborneol, and γ-terpinene have shown potent antifungal activity (Moon et al. 2018).

1.7.4 Phenolic Compounds

Phenolic compounds, also called nonvolatile compounds, are drawn from fresh ginger. Gingerol derivatives (6-gingerol, 8-gingerol, 10-gingerol), 1-dehydro-6-gingerdione, diacetoxy-8-gingerdiol, shogaols, zingerone, and paradols are the major constituents and impart pungent taste to ginger. Gingerols can be converted into corresponding shogaols through heating or long-term storage, while paradols can be obtained from shogaols by hydrogenation process (Asamenew et al. 2019; Stoner 2013). Shogaols are responsible for the pungent taste of dry ginger (Lee et al. 2007). Besides these constituents, some pungent compounds including shogaol and gingerol have also been reported in ginger root and also possess anthelmintic activity (Lin et al. 2014). In addition, zingerone, gingerenone, quercetin, and 6-dehydrogingerdione are the other phenolic compounds found in ginger (Ji et al. 2017; Schadich et al. 2016).

1.7.5 Other Chemical Constituents

Chemical investigation on ginger rhizomes (*Z. officinale*) has also detected some other novel compounds including beta-sitosterol palmitate, hexacosanoic acid 2,3-dihydroxypropyl ester, isovanillin, glycol monopalmitate, adenine, and 1-(omegaferuloxyceratyl) glycerol (Bao et al. 2010).

1.7.6 Proteins and Amino Acids

Zingiber officinale is composed of many amino acids such as glycine, alanine, cysteine, valine, aspartic acid, threonine, lysine, arginine, proline, tyrosine, phenylalanine, histidine (He and Li 2012), and tryptophan (Liu et al. 2019).

1.7.7 Carbohydrates

Ginger is rich in soluble sugar and polysaccharides (Liu et al. 2019).

1.7.8 Organic Acids

Ginger constitutes a number of acids including oxalic acid, tartaric acid, lactic acid, acetic acid, citric acid, and malonic acid (Li et al. 2006; Liu et al. 2019).

1.7.9 Inorganic Components

In addition to sugar, proteins, and organic acids, *Zingiber officinale* contains K, Mg, Ga, Mn, P, Al, Zn, Fe, and Ba as inorganic compounds (Liu et al. 2019).

1.8 Pharmacological Potentials

Zingiber officinale Roscoe is a worldwide recognized medicinal plant in many traditional systems as mentioned above for wide array of maladies including inflammation, fever, constipation, cold, hypertension, dementia, and many more (Poprac et al. 2017). Recently, extensive literature survey has demonstrated the establishment of scientifically proven pharmacological potentials of ginger extracts as well as its isolated active chemical constituents. Ginger has immense number of biological properties (Fig. 1.4) including antioxidant, anti-inflammatory, antitumor, antibacterial, anticancer, neuroprotective, antiulcer, antiemetic, antihypertensive, and so on which are illustrated in detail one after other below.

1.8.1 Antioxidant Activity

Oxidative stress arises due to overproduction of free radicals which may induce severe health-related issues in human beings. Therefore, medicinal plants with promising antioxidant activity may have key role in reducing oxidative stress (Ali et al. 2008a; Poprac et al. 2017). One such plant amid several medicinal plants is *Zingiber officinale* (ginger). Ginger and its chemical constituents exhibit notable antioxidant activity primarily through inhibition of ascorbate/ferrous complex located in hepatic microsomes (Mele 2019; Rahmani et al. 2014). Approximately 40 antioxidant molecules, for instance, zingerone, gingerols, shogaols, etc., have been recorded to exert antioxidant effect (Chrubasik et al. 2005; Kikuzaki and Nakatani 1996). Interestingly, the antioxidant activity of various gingers like dried, fresh, stir fried, and carbonized varies in the following order dried ginger > stir-fried ginger > carbonized ginger > fresh ginger. Fresh ginger has poor antioxidant effect due to high moisture content and low polyphenolic contents. On the other side, antioxidant activity of dried ginger is further reduced due to heating process and transformation of gingerols to shogaols (Li et al. 2016). Several antioxidant studies of ginger and its active constituents using various assays have been summarized in Tables 1.4 and 1.5. The antioxidant potential of ginger is associated with the

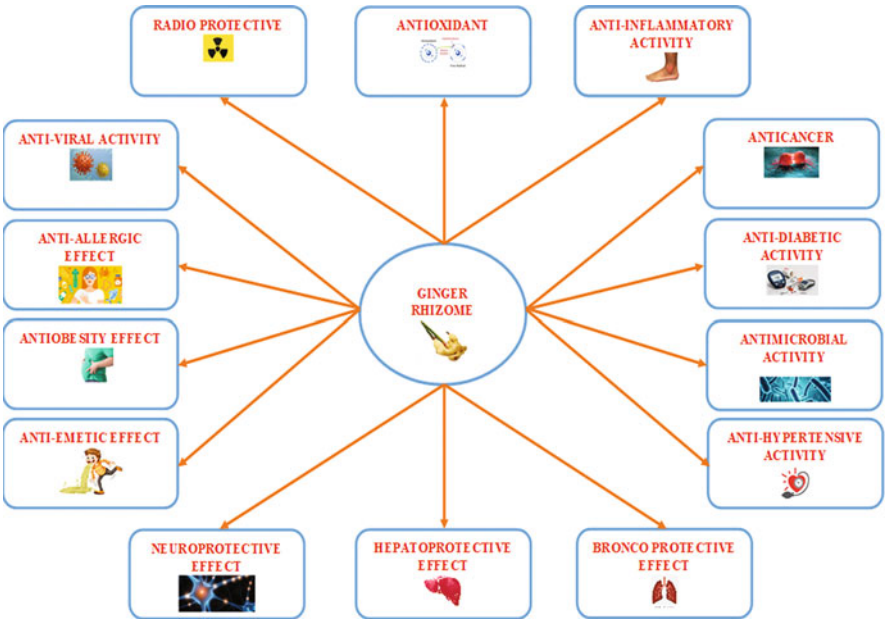

Fig. 1.4 Pharmacological effects of ginger and its chemical constituents

prevention and management of numerous conditions such as cancer, cardiovascular disorders, atherosclerosis, neurological disorders, etc. (Semwal et al. 2015).

1.8.2 Anti-Inflammatory Activity

Inflammation refers to a defensive response in the body against harmful stimuli such as physical, chemical, mechanical, and environmental toxins. Abnormal responses, however, manifest into a wide range of chronic ailments, for example, cardiovascular disease, autoimmune disease, metabolic syndrome, cancer, and so on (Ghasemian et al. 2016). In addition, oxidative stress also triggers inflammatory events in the body tissues. Recently, ginger and its constituents have shown significant anti-inflammatory effects. Ginger effectively alleviate inflammation through several mechanisms including inhibition of cyclooxygenase (COX) and lipooxygenase (LOX) and regulation of prostaglandins, interleukins, cytokines, nitric oxide, etc. (Gunathilake and Vasantha Rupasinghe 2015; Mele 2019). Moreover, anti-inflammatory and antiproliferative effects of ginger can also be mediated through cell signaling molecules including p38/MAPK, p65/NF-kB, Bax/Bcl2, Nrf2, TNF-α, SAPK/JNK, ERK1/2, caspase-3, caspase-9, and p53 (de Lima et al. 2018).

A research conducted with ointment prepared from ginger extract has shown promising anti-inflammatory and antinociceptive activities on AITC-induced model. Notably, ointment at concentration 0.025% has shown superior anti-inflammatory

Table 1.4 Antioxidant potential of ginger extracts

Extracts	Assay/subject	Standard	Mechanism	Reference
Ethanol	2,2-diphenyl-1-picryl-hydrazyl (DPPH) free radical scavenging, thiobarbituric acid reactive substances	Butylated hydroxyl toluene (BHT)	Inhibition of hydroxyl radicals	Stoilova et al. (2007)
Ethanol and methanol	DPPH free radical scavenging, hydrogen peroxide scavenging, reducing power assay	BHT, BHA, tocopherol, ascorbic acid	–	Yesiloglu et al. (2013)
Soya bean oil containing ginger extract (2500 mg/kg)	–	–	Inhibits lipid peroxidation and increases the shelf life of food	Jorge and Andreo (2013)
Fresh, dried, stir-fried, and carbonized gingers	DPPH, ferric reducing antioxidant power (FRAP)	–	–	Li et al. (2016)
Ginger extract	Cancer patients		Enhanced the levels of antioxidant enzymes such as SOD, CAT, and GPx and GSH/GSSG	Danwilai et al. (2017)
Aqueous and methanolic extract (250, 500 mg/kg)	Radical scavenging activity, β-carotene bleaching, reducing power assay	BHA, ascorbic acid	Prevent lipid peroxidation	Bekkouch et al. (2019)
Polyphenolic-rich fraction of dry ginger powder	FRAP, oxygen radical absorbance capacity (ORAC), and cellular antioxidant activity		Inhibits isolated digestive enzymes	Sakulnarmrat et al. (2015)
Ethyl acetate, ethanol diethyl, ether *n*-butanol, and aqueous extracts	DPPH, FRAP, and H_2O_2 assay		Inhibited xanthine oxidase, lipoxidase β-glucuronidase, and hyaluronidase activities	Nile and Park (2015)

response. These responses of ginger can be due to the binding of active phytochemicals to TRPA1 and TRPV1 ion channels (Kravchenko et al. 2019). Moreover, various extracts obtained from ginger rhizome, callus, and callus treated with some elicitors such as glycine and salicylic acid significantly suppressed the LPS-induced chemical mediators like IL-1, IL-6, and TNF-α, thereby eliciting a

Table 1.5 Antioxidant potential of isolated chemical constituents of ginger

Chemical constituent	Subjects	Underlying mechanisms	References
Ginger oleoresin (100 mg/kg)	Human mesenchymal stem cells	Reduces ROS production Promotes the translocation of Nrf2 to the cell nucleus	Ji et al. (2017)
6-Shogaol (20 μM)	HCT-116 human colon cancer cells	Increases the intracellular GSH/GSSG ratio Slows down the level of ROS	Chen et al. (2014)
Ginger phenylpropanoids (40 μg/mL)	BJ foreskin fibroblasts	Increase in Nrf2 activity and GSTP1 level	Schadich et al. (2016)
Gingerol-related compounds	DPPH and 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH) method	Inhibitory effects against autoxidation of oils and the AAPH-induced peroxidation of liposome	Masuda et al. (2004)
6-Gingerol and 6-Shogaol	DPPH, ABTS	–	Ali et al. (2018)
Zingerone	–	Inhibited the formation of $ONOO^-$-mediated tyrosine nitration	Aeschbach et al. (1994) and Shin et al. (2005)

protective response against inflammatory conditions (Ali et al. 2019). There are some other reports on anti-inflammatory activity of ginger and its principle constituents as depicted in Table 1.6 (Mao et al. 2019).

1.8.3 Anticancer Activity

Cancer, a life-threatening condition, is distinguished by uncontrolled proliferation of normal human cells. Despite considerable research in drug development, there is constant demand of herbal drugs to fight with this challenging disease (Akindele et al. 2015; Nguyen et al. 2020). It has been reported that about 60% of drugs isolated from natural sources are being employed in the treatment of cancer (Gordaliza 2007). Notably, oxidative stress is a potential hallmark of cancer induction. Numerous cellular events like cell proliferation and signaling pathways including growth factors and mitogenic pathways are mediated through ROS and eventually lead to progression of carcinogenesis (Nourazarian et al. 2014). Ginger rhizome has around 50 antioxidants and thus exhibits anticancer property against various types of cancers (Ansari et al. 2016; Masuda et al. 2004). Although, ginger and its derivatives inhibit numerous kinds of cancers including colon, breast, renal, ovarian, brain, and prostate cancers, data gathered from in vitro and in vivo experiments have indicated that ginger is extensively used in the treatment of gastrointestinal cancers (Table 1.7) (Prasad and Tyagi 2015). More recently, a comparative anticancer activity of free ginger phenolics (GPs) and conjugated GPs was investigated in various in vitro and

Table 1.6 Anti-inflammatory activity of ginger extracts and its constituents

Extract/ constituent	Dose	Model/cell lines	Mechanisms
Ginger extract	50 mg/mL	C57BL6/J mice	Activates Akt and NF-kB
Ginger extract and zingerone	0.1, 1, 10, and 100 mg/kg	Female BALB/c mice	Inhibit NF-kB activation Suppress the level of IL-1β and TNF-α
6-Gingerol-rich fraction	50 and 100 mg/kg	Female Wistar rats	Enhances myeloperoxidase, NO, and TNF-α levels
6-Shogaol	100 μM	HT-29/B6 and Caco-2 Human intestinal epithelial cells	Inhibits the PI3K/Akt and NF-$_k$B signaling pathways
6-Shogaol and 6-Gingerol, 6-Dehydroshogaol	2.5, 5, and 10 μM	RAW264.7 mouse Macrophage cells	Inhibit NO and PGE2 synthesis
GDNPs 2	0.3 mg	Female C57BL/6 FVB/NJ mice	Increases IL-10 and IL-22 levels; Decreases TNF-α, IL-6, and IL-1 levels

xenograft mouse models. The findings showed that, relative to normal cells, selective over-expression of β-glucuronidase (β-gd) in cancer cells enabled the conversion of conjugated glucuronides into free forms of tumor tissue. In vitro studies confirmed that the free forms are more cytotoxic compared to the glucuronide conjugates (Mukkavilli et al. 2018). Several molecular mechanisms such as upregulation of suppressor gene, apoptosis, induction, and inactivation of vascular endothelial growth factor (VEGF) have been implicated in anticancer activity of ginger (Rahmani et al. 2014). In addition, various signaling molecules including Bcl-2, caspases, NF-κB, TNF-α, COX-2, STAT3, MAPK, PI3K Akt, cyclin D1, survivin, cIAP-1, and other regulatory proteins are responsible for anticancer activity of ginger (Prasad and Tyagi 2015).

1.8.4 Antidiabetic Activity

Diabetes mellitus (DM), an endocrine disorder, is marked by elevated blood glucose level owing to inadequate insulin arising from impaired metabolic pathways. Polyurea (excessive urine production), polyphagia (increased hunger), and polydipsia (excessive thirst) are the salient features of DM (Otunola and Afolayan 2019). Microvascular (neuropathy, nephropathy, and retinopathy) and macrovascular (stroke, heart attack) are the main complications exacerbated by DM (Patel et al. 2012). Although several classes of antidiabetic agents are available including sulfonylureas, non-sulfonylureas secretagogues, biguanides, α-glucosidase inhibitors, and thiazolidinediones with their unique mechanisms, they possess severe

Table 1.7 Anticancer effects of ginger extracts and constituents

Extract/constituents	Cancer type	Mechanism	Reference
Ginger extract	Gastric cancer	• Decreasing the gastric ulcer area • Decreasing the level of xanthine oxidase, myeloperoxide, and malondialdehyde • Prevent gastric mucosal damage through antioxidant property	Ko and Leung (2010)
6-Gingerol	Gastric cancer	• Induces the apoptosis of gastric cancer cells • Facilitates apoptosis by increasing caspase 3/7 activation • Mediates downregulation of cytosolic inhibitor of apoptosis (cIAP)-1 • Inhibits nuclear factor-kappa B (NF-kB)	Ishiguro et al. (2007)
6-Shogaol	Gastric cancer	• Suppresses the survival of gastric cancer cells through microtubules damage	Ishiguro et al. (2007)
Ginger extract	Gastric cancer	• Chemosensitizing effect in neoplastic cells in vivo and in vitro	Sharma and Gupta (1998)
Zerumbone	Gastric cancer	Inhibits cell proliferation, VEGF expression, and NF-kB activation	Tsuboi et al. (2014)
6-Gingerol	Pancreatic cancer	• Inhibits the growth of pancreatic cancer cells at G1 Phase • Reduced both cyclin A and cyclin-dependent kinase (Cdk) expression • Reduces retinoblastoma phosphorylation and blocking of S-phase entry • Inhibition of NF-kB/snail through ERK (extracellular signal-regulated kinases) pathway	Kim and Kim (2013) and Park et al. (2006)
6-Shogaol	Pancreatic cancer	• Trigger ca^{++} signals in the pancreatic β cells by activating the TRPVI channels • Suppression of NF-kB, COX-2, cyclin D1, survivin, cIAP-1, Bcl-2, matrix metallopeptidase • Decrease in proliferation index (Ki-67)	Rebellato and Islam (2014) and Siegel et al. (2014)
6-Shogaol	Liver cancer	• Induce apoptotic cell death via oxidative stress-mediated caspase-dependent mechanism	Chen et al. (2007)
Gingerol	Liver cancer	• Decreases the levels of SOD, GSH, glutathione reductase and glutathione-S-transferase, glutathione peroxidase	Jeena et al. (2013)

(continued)

Table 1.7 (continued)

Extract/constituents	Cancer type	Mechanism	Reference
Ginger extract	Liver cancer	• Alters the cellular morphology such as cell shrinkage and condensation of chromosome in HepG2 cells	Vijaya Padma et al. (2007)
6-Gingerol	Liver cancer	• Induces apoptosis in HepG2 cells through lysosomal mitochondrial axis	Yang et al. (2012)
Ginger extract	Liver cancer	• Inhibits the development of diethyl nitrosamine-induced premalignant phenotype in rat hepatocarcinogenesis Restores the serum hepatic tumor markers in rats	Mansour et al. (2010)
6-Shogaol	Liver cancer	• Activation of caspase-3 and inactivation of $eIF_2\alpha$	Hu et al. (2012)
Ginger extract	Liver cancer	• Inhibits cytochrome p450 enzyme	Mukkavilli et al. (2014)
Zerumbone	Liver cancer	• Stimulates phase-II detoxification enzymes in hepatic epithelial cell line • Exerts antioxidant effects by inducing nuclear localization of the transcription factor	Nakamura et al. (2004)
6-Gingerol	Colorectal cancer	• Inhibition of leukotriene A4 hydrolase activity	Radhakrishnan et al. (2014)
		• Induces apoptosis through protein degradation and downregulation of cyclin D1, PKC epsilon, and GSK-3β-pathways	Lee et al. (2008)
Ginger extract	Colorectal cancer	• Slows down the levels of fecal bile acid, sterols, cholesterol, HMGCoA reductase, free fatty acids, phospholipase A and C • Suppresses tumor growth in nude mice in vitro	Manju et al. (2006) and Radhakrishnan et al. (2014)
Shogaol conjugated with cysteine	Colorectal cancer	• Activation of the mitochondrial apoptotic pathway	Fu et al. (2014)
Hexahydrocurcumin	Colorectal cancer	• Induces apoptosis to SW480 colon cancer cells at G_1/G_0 phase	Chen et al. (2011)
Ginger leaf extract	Colorectal cancer	• Exhibits reduced cell viability • Increases ATF3 expression through ERK1/2 activation	Park et al. (2014)

adverse effects. Hence, the drugs obtained naturally are being preferred over synthetic medicines for DM management (Salehi et al. 2019). A significant number of medicinal plants have found their usefulness as a solution to the treatment of diabetes

and some of its associated complications. Ginger is one such plant used for diabetic condition. Accumulated evidences have shown that ginger is extensively investigated for its hypoglycemic effect as summarized in Table 1.8.

1.8.5 Antimicrobial Activity

Microbial infections have become a major threat across the world nowadays. A wide range of bacterial agents can cause and even result in death from serious infections (Rahmani et al. 2014). The most pathogenic bacteria include extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, carbapenem-resistant *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* (Marasini et al. 2015). It is worthy to mention that self-medication, wide distribution of antimicrobial agents, uncertain diagnosis, and the absence of rational antimicrobial programs strongly contribute to bacterial resistance and making them ineffective. Therefore, search for novel antimicrobial agents to combat microbial infections is urgently required. Currently, natural products have been advocated as a possible option for the substitution of synthetic antimicrobial drugs (Teles et al. 2019).

The most commonly employed methods for antimicrobial activity are disk and well agar diffusion and agar and broth microdilution techniques. The findings obtained from disk and well diffusion methods, however, indicate superior antimicrobial activity over agar diffusion test. The solubility of all GEO components is assumed to be better in the disk diffusion method, while the diffusion of oil in the agar restricts the use of the agar diffusion method (Teles et al. 2019). A recent study has demonstrated the development of nanoemulsions from ginger leaves essential oil (GLEO) which was tested for its antimicrobial activity against *Streptococcus mutans*. Clindamycin was used as standard drug. The MIC value was found to be 62.5 μL/mL (Mostafa 2018). Several other evidences have demonstrated the antimicrobial potential of ginger rhizome extracts and GEO against various microorganisms using in vitro and in vivo assays, as can be seen in Tables 1.9 and 1.10, respectively.

1.8.6 Antihypertensive Activity

Hypertension (HTN), also referred to as high blood pressure, is caused due to elevation of blood pressure in the arteries. It is the major cause of morbidity and mortality, causing nearly 9.4 million deaths globally. HTN also results in cardiovascular and renal complications. Although traditional antihypertensive agents have been used to treat hypertension, such agents are associated with poor efficacy and serious side effects including dizziness, emotional distress, GIT disturbances, dry mouth, and visual problems (Sultana and Asif 2017; Tabassum and Ahmad 2011). In order to treat this chronic disease, medicinal plants have gained tremendous attention, and ginger is an interesting example of such an herb. In a study, treatment with

Table 1.8 Antidiabetic potential of ginger extracts and phytoconstituents

Extracts/ constituents	Dose (mg/kg)	Model	Results	Reference
Hydroalcoholic extract	200 and 400	Streptozotocin-induced diabetic rats	• Decrease in blood glucose level • Downregulation of arginase-1 activity and expression • Increase in serum insulin	Lamuchi-Deli et al. (2017)
Aqueous extract	500 and 1000	Alloxan monohydrate-induced diabetic rats	• Lowers blood glucose level • Repairs damaged pancreas	Al-Qudah et al. (2016)
Hydroethanolic extract	250	High-fat diet (HFD) in rat model	• Improved lipid profile • Attenuated blood glucose insulin and lipid level	de Las Heras et al. (2017)
Raw and cooked ginger extract		Streptozotocin-induced diabetic liver injury in rats	• Reduction in blood glucose level	Oludoyin and Adegoke (2014)
Ginger powder, aqueous methanolic extract, and ginger oil	200	Streptozotocin-induced diabetic rats	• Lower blood glucose level • Reduction in level of SGPT and SGOT, alkaline phosphatase (ALP), lipid profile (cholesterol and total lipid)	Anfenan (2014)
Aqueous extract of raw ginger	500	Alloxan-induced and insulin-resistant diabetic rats	• Reduction in fasting blood glucose and malonaldehyde levels • Enhances insulin synthesis	Iranloye et al. (2011)
Fresh ginger extract	500	Alloxan-induced diabetes in rats	• Reduction in total cholesterol, LDL, and blood glucose level	Al-Noory et al. (2013)
Aqueous extract	500	Streptozotocin-induced diabetic rats	• Reduced glucose level in liver and skeleton muscles • Increased glucose level in kidney • Increased enzymatic activity of glycolytic enzymes (glucokinase, phosphofructokinase, and pyruvate kinase)	Abdulrazaq et al. (2012)
Ginger ethanolic extract	100, 200, and 400	HFD-fed rat model	• Reduction in glucose, total cholesterol, LDL, triglycerides, free fatty acids, and phospholipids in serum	Nammi et al. (2009)

(continued)

Table 1.8 (continued)

Extracts/ constituents	Dose (mg/kg)	Model	Results	Reference
Raw ginger	500	Streptozotocin-induced diabetic rats	• Lowers glucose, cholesterol, and triglycerol level in serum • Reduction in urine protein	Al-Amin et al. (2006)
Ethanolic extract	200	Streptozotocin-induced diabetes in rats	• Increase in HDL level • Exhibit lipid-lowering activity	Bhandari et al. (2005)
Aqueous extract	500	Streptozotocin-induced diabetic liver injury in rats	• Lowers blood glucose level • Restoration of hepatic enzymes presented total antioxidants near normal values in serum	Otunola and Afolayan (2015)

petroleum ether extract of ginger (50 mg/kg) and its toluene fraction (10 mg/kg) caused significant reduction in blood pressure in fructose- and deoxycorticosterone acetate (DOCA)-induced hypertensive rats (Mahalaxmi et al. 2007). Furthermore, antihypertensive effect of *Zingiber officinale* extract (ZO) was assessed in healthy human subjects. The findings revealed a marked decrease in the heart rate and increase in only the systolic blood pressure after oral administration with ZO extract at dose 100 mg/kg (Ojulari et al. 2014). Another research determined the underlying mechanism of ginger varieties involved in hypertension. The outcomes revealed that aqueous extracts of red ginger and white ginger had inhibitory effect on angiotensin-I-converting enzyme (ACE) and some pro-oxidants induced by lipid peroxidation in rat heart in vitro. Nevertheless, inhibitory effect of red ginger was found greater than that of white ginger (Akinyemi 2013). In addition, hypotensive and vasodilator effects of ginger and phenolic compounds were evaluated along with the underlying mechanism involved. The phenolic constituents, namely, 6-, 8-, and 10-gingerol, exhibited a promising atropine-resistant vasodilator activity, while the aqueous extract caused substantial reduction in blood pressure through inhibition of Ca^{++} ion channels and stimulation of muscarinic receptors (Ghayur et al. 2005). Recently, randomized and quasi-randomized controlled trials on humans have shown that ginger extract (100 mg/kg) significantly reduced systolic BP from 114.3 ± 3.22 mmHg to 105.5 ± 3.13 and diastolic BP from 73.3 ± 3.35 mmHg to 70.5 ± 3.39 mmHg within 2 h. However, future studies require more human trials on antihypertensive effect of ginger extracts using different dosage (Torabi et al. 2017).

Table 1.9 In vitro antimicrobial activity of ginger extracts (Ashokkumar et al. 2020a; b)

Extract	Microorganisms	Standard drug
Aqueous extract	*Helicobacter pylori*	Lansoprazole
	C. albicans	–
	K. pneumoniae *Proteus vulgaris* *P. mirabilis* *B. subtilis* *C. albicans* *E. coli*	Amracin (for bacteria) Nystatin (for yeast)
	B. subtilis *K. pneumoniae* *P. mirabilis* *S. aureus* *P. aeruginosa* *E. coli*	–
Ethanolic extract	*E. coli*	Ciprofloxacin
	Klebsiella sp. *Enterobacter* sp.	Ciprofloxacin
	S. aureus *Bacillus* sp. *Proteus* sp.	Ciprofloxacin
	C. albicans	–
	B. subtilis *K. pneumoniae* *P. mirabilis* *S. aureus* *P. aeruginosa* *E. coli*	–
	P. aeruginosa *B. subtilis*	–
Methanol extract	*E. coli* *S. aureus* *E. faecalis* *C. albicans* *M. smegmatis* *S. mutans*	–
	B. subtilis *K. pneumoniae* *P. mirabilis* *S. aureus* *P. aeruginosa* *E. coli*	–
Chloroform extract	*E. faecalis* *S. mutans* *C. albicans* *M. smegmatis* *E. coli* *S. aureus*	–
Ethyl acetate extract	*S. aureus* *S. mutans*	–

(continued)

Table 1.9 (continued)

Extract	Microorganisms	Standard drug
	E. faecalis *C. albicans* *E. coli* *M. smegmatis*	
Petroleum ether extract	*S. aureus* *C. albicans* *S. mutans*	–
Subcritical extract	*K. pneumoniae* *Proteus vulgaris* *P. mirabilis* *B. subtilis* *C. albicans* *E. coli*	Amracin (for bacteria) Nystatin (for yeast)
Acetone extract	*B. subtilis* *K. pneumoniae* *P. mirabilis* *S. aureus* *P. aeruginosa* *E. coli*	–

Table 1.10 Antimicrobial activity of ginger essential oil (GEO)

Component	Microorganisms	Standard drug
GEO	*Bacillus subtilis*	Tetracycline
	Staphylococcus aureus	–
	Vibrio vulnificus *V. parahaemolyticus* *Pseudomonas aeruginosa* *Yersinia enterocolitica*	Ampicillin
	Salmonella typhimurium *S. paratyphi* *E. coli*	Ampicillin
	Candida albicans	Fluconazole
	Fusarium verticillioides	–
	Botrytis cinerea *Alternaria panax* *F. oxysporum*	–
	Fusarium verticillioides	–
	Aspergillus niger *M. hiemalis* *F. oxysporum*	–
	Aspergillus flavus *Penicillium expansum*	–
Oleoresin	*S. aureus*	–
	Penicillium spp.	–

1.8.7 Broncho-Protective Effects

In recent decades, high prevalence of asthma has become a global burden affecting both rural and urban communities. Asthma is a respiratory disorder characterized by inflammation of the airways, bronchoconstriction, and increased airway hyperresponsiveness (Singh et al. 2007). Genetic and environmental changes are the two major risk factors associated with asthma (Schafer 1997). Despite a wide range of asthma therapies, for example, β-agonists and corticosteroids, some effective and safe therapeutic approaches including herbal drugs are more delighted. Nowadays, herbal medicines as effective and safe therapeutic approaches are more encouraged amid a broad variety of asthma treatments (Singh et al. 2007). Ginger is one such herbal remedy for asthma. Ginger (150 mg) relieves form wheezing and chest tightness and reduces the asthmatic symptoms but ineffective in changing the disease stage (Rouhi et al. 2006). Moreover, the broncho-protective potential of aqueous extract of *Zingiber officinale* rhizome was assessed in histamine-induced bronchospasm in guinea pigs. In this study, salbutamol and chlorpheniramine maleate were used as standard drugs. The treatment with ginger extracts at doses 200, 400, 600, and 800 mg/kg produced remarkable antiasthmatic activity in experimental animals (Rout et al. 2010). In another study, a significant bronchodilation was observed by ginger and its active constituents, namely, 6-gingerol, 8-, gingerol, and 6-shogaol, by modulating intracellular Ca^{++} ion in airway smooth muscle (Townsend et al. 2013). Recently, a randomized, double-blind placebo-controlled clinical study has shown significant reduction in inflammation and asthma-related inflammatory markers in serum by oral consumption of ginger at a dose of 2 g per day. The antiasthmatic activity of ginger can be attributed to its anti-inflammatory and antioxidant effects and attenuation of allergic response (ClinicalTrials.gov Identifier: NCT03705832) (Emala and Dimango 2020). In ovalbumin-induced allergic asthma model, ethanol and aqueous ginger extracts effectively suppressed allergic inflammation possibly through inhibiting Th2-mediated immune response which was further confirmed by decrease in mRNA expression levels of IL-4 and IL-5 (Khan et al. 2015). Recent study has demonstrated that the antiasthmatic effect of ginger and its constituent, namely, 6-shogaol, is linked with acute airway smooth muscle relaxation and chronic inhibition of inflammation (Yocum et al. 2020). Ginger can therefore be regarded as a well-known herbal remedy for the treatment of respiratory disorders, including asthma.

1.8.8 Hepatoprotective Effects

Liver plays a vital function in various physiological processes including metabolism and detoxification of drugs. Liver diseases have been a significant health issue worldwide for the last few decades. Several factors including environmental pollutants, exposure to toxic chemicals, consumption of alcohol, and medications are the major concern of liver ailments (Atta et al. 2010; Koek et al. 2007). Therefore, greater emphasis is being focused toward the use of medicinal plants as

hepatoprotective agents as the available synthetic drugs exhibit serious side effects (Mujeeb et al. 2011). The hepatoprotective potential of ginger extracts has been extensively reported as can be seen in Table 1.11. The active constituents of ginger, however, have not yet been investigated to date. Thus, there is also an urgent need to explore the protective effects of active constituents of ginger against liver injury.

1.8.9 Neuroprotective Effects

In the current century, cognitive dysfunction and many other neurological disorders including depression, schizophrenia, Alzheimer's disease, Parkinson's disease, and dementia are the leading cause of death globally. Approximately, 8% total deaths and 2 in 1000 cases have been reported due to these neurological disorders (Kumar and Khanum 2012). Neuroprotection refers to the approaches and related mechanisms applied to protect the central nervous system against neuronal injury arising due to acute and chronic neurodegenerative disorders (Uddin et al. 2013). A plethora of natural products from plants have been exploited for the treatment of neurological disorders (Uddin et al. 2013). Ginger is an excellent neuroprotective candidate amid medicinal plants. Several reports have detailed the neuroprotective effects of ginger which can be credited to its phenolic and flavonoid constituents (Mele 2019). In monosodium glutamate (MSG)-induced neurotoxicity model, ginger (500 mg/kg) has shown protective effects via reduction of DNA oxidative marker 8-hydroxy-2-deoxyguanosine (8-OHdG) and β-amyloid accumulation and alteration in neurotransmitter levels (Hussein et al. 2017). Recent study has demonstrated a remarkable improvement in memory and cognitive dysfunctions by oral supplementation of 6-gingerol (25 mg/kg) in scopolamine-induced amnesia in C57BL/6 mice. Furthermore, 6-gingerol increased the protein expression of brain-derived neurotrophic factors (BDNF) via activation of protein kinase B/Akt- and c AMP-response element binding protein (CREB) signaling pathway (Kim et al. 2018a). More recently, ginger extract (50 mg/kg) exhibited neuroprotection in traumatic brain injury model by enhancing BDNF and growth-associated protein-43 (GAP-43) in the brain and lowering the levels of NF-κB, IL-1b, and glial fibrillary acidic protein (GFAP) (Sahin et al. 2019). Thus, it can be suggested that neuroprotective potential of ginger is associated with its antioxidative and anti-inflammatory activities.

Zingiber officinale rhizome extract ameliorated cognitive functions and memory performance against oxidative stress-related brain damage and memory deficit induced by focal cerebral ischemia (Wattanathorn et al. 2011). In another study, intraperitoneal injection of ginger root (100 mg/kg) enhanced the level of different neurotransmitters (epinephrine, norepinephrine, dopamine, and serotonin) possibly due to inhibition of 5HT-3 receptors and Ca^{++} ion channels (Waggas 2009). Besides, anti-oxidant defense mechanism and downregulation of MDA level have also been implicated in neuroprotection against streptozotocin-induced diabetic rats (Shanmugam et al. 2011). Reduction in AChE expression and improvement in

Table 1.11 Hepatoprotective potential of ginger extracts

Extract/ constituent	Dose (mg/kg)	Model	Standard	Effect	Reference
Methanol	250 and 500	Carbon tetrachloride intoxication in rats	25 mg/kg silymarin	Decreases the activity of ALP and GGT	Atta et al. (2010)
Ethanolic	250 and 500	Thioacetamide-induced hepatotoxicity in rats	Silymarin	Reduction in the levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, globulin, total bilirubin, and conjugated bilirubin Increases albumin content	Abdulaziz Bardi et al. (2013)
Aqueous infusion	100, 200, and 400	Paracetamol-induced hepatotoxicity in rats	Silymarin (25 mg/kg)	Reduction in ALT, AST, ALP, and total bilirubin	Yassin Nemat et al. (2010)
Ginger extract		Piroxicam-induced liver toxicity		Decrease in ALT, ALP, and immune-expression of the proapoptotic protein (Bax)	Huang (2019)
Dry ginger and essential oil	–	Diethylnitrosamine (DEN) toxicity in rats	–	Decrease in serum ALT and ALP Increase in serum GSH-Px activity	Hassanen et al. (2020)
Ethanolic extract	200	Country-made liquor (CML)-induced liver injury in rats	Silymarin (25 mg/kg, orally)	Lowering of serum AST, ALT, ALP, g-GTP, and tissue lipid peroxide levels	Bhandari et al. (2003)
Ginger extract	100	Acetaminophen-induced acute hepatotoxicity in rats	–	Lowering of AST, ALT, ALP, arginase, and total bilirubin reduction in oxidative stress by inhibiting lipid peroxidation	Abdel-Azeem et al. (2013)
Ginger seed solution	500	Mercury-induced hepatotoxicity in female rats	–	Cure and protect the liver against damage already caused by the mercury	Ezeasuka et al. (2015)

neurogenesis may also contribute to neuroprotective effect of ginger (El-Akabawy and El-Kholy 2014).

The cytoprotective effect of 6-dehydrogingerdione against oxidative stress-induced neuronal cell damage has been reported (Yao et al. 2014). In addition, neuroprotective activity was also shown by another molecule, namely, 6-shogaol, by activating Nrf2 and elevating the levels of several phase II antioxidant molecules such as NQO1 and HO-1, in rat pheochromocytoma PC12 cells (Peng et al. 2015). There are fewer reports on neuroprotective effect of ginger's constituents; hence much more investigations are needed to explore the role of active constituents of ginger as neuroprotective agents.

1.8.10 Antiemetic Effects

For over thousands of years, ginger has been used to alleviate a number of gastrointestinal symptoms, including nausea, vomiting, diarrhea, and dyspepsia. Recent research has demonstrated that this spice is extensively investigated in various indications associated with nausea and vomiting such as nausea and vomiting in pregnancy (NVP), post-operative nausea and vomiting, and chemotherapy-induced nausea and vomiting (CINV); however, limited investigations have been explored in the case of motion sickness (Lete and Allué 2016; Palatty et al. 2013). Nausea and vomiting are complex mechanisms whose symptoms are affected by the emetogenic response and stimuli. Ginger has been documented to elicit antiemetic effects against a number of emetogenic stimuli (Palatty et al. 2013). In a study, intraoperative nausea episodes were suppressed by dry ginger powder in elective cesarean section patient (Jin et al. 2014). Ginger aqueous extract and its pungent constituents have also been reported to alleviate from nausea and emesis. In chemotherapy-induced emesis model, 6-shogaol, 6-gingerol, and zingerone exhibited remarkable antiemetic effect via inhibiting emetic signal induced by 5-HT (Jin et al. 2014). Another experiment demonstrates that antiemetic effect of ginger was due to inhibition of 5-HT_3 receptors located in enteric neurons (Walstab et al. 2013). Furthermore, ginger was shown to prevent antiretroviral-induced nausea and vomiting episodes in a randomized clinical trial (Dabaghzadeh et al. 2014). In addition, ginger is a potential candidate for alleviating antituberculosis drug-induced gastrointestinal nausea and vomiting in patients with tuberculosis (Emrani et al. 2016). Though exact mechanisms implicated in antiemetic activity of ginger are still unraveled, ginger and its active components are believed to act by enhancing the gastric tone and motility mediated through antiserotonergic and anticholinergic actions within GIT (Abdel-Aziz et al. 2006). In addition, ginger is also reported to increase gastric emptying and thus relieves from gastrointestinal troubles including emesis (Hu et al. 2011).

1.8.11 Antiobesity Effects

Obesity is a complex medical condition associated with several health problems such as cardiovascular diseases, diabetes, hepatic disorders, inflammatory disease (osteoarthritis), hypertension, and some cancers (Kim et al. 2018b; Patra et al. 2015). Energy imbalance (energy intake and energy expenditure) is a key factor in the development of obesity contributing to a massive amount of fat in the body tissues (Nderitu et al. 2017). Recently, ginger and its active components have been taken into consideration for the treatment of obesity (Ebrahimzadeh Attari et al. 2018). There are several reports that indicate effectiveness of ginger in the management of obesity. In vitro experiment in mice fed a HFD has shown that administration of 3% *Zingiber officinale* water extract caused substantial reduction in parametrial adipose tissue weight which might be attributed to the inhibition of intestinal absorption of dietary fat by the active constituents of ginger (Han et al. 2005). On the other hand, dried ginger powder induces fat utilization by enhancing fat oxidation in humans (Miyamoto et al. 2015). Furthermore, inhibitory effects on adipogenesis and lipid accumulation were also shown by gingerenone A (Suk et al. 2017). Other pungent constituents, namely, 6-shogaol and 6-gingerol, have shown an increase in cellular acid metabolism via increasing peroxisome proliferator-activated receptor δ (PPAR δ)-dependent gene expression (Misawa et al. 2015). In addition, high-fat diet-induced metabolic disturbances were protected by ginger extract by reducing the body weight, oxidative stress, and hyperlipidemia (Bin-Meferij et al. 2017). Another research revealed that high-hydrostatic pressure extract of ginger (8 g/kg) more effectively reduces obesity and inflammation than hot water extract possibly through downregulation of miR-21/132 expression and AMPK activation (Kim et al. 2018b). Moreover, ginger could alter the gene expression and protein levels of some brown and beige adipocyte markers, and this resulted in the enhancement of brown tissue function and activates white adipose tissue (Wang et al. 2019). More recently, in a randomized, double-blind study, steamed ginger ethanolic extract (SGE) effectively reduced body weight and fat mass in healthy obese patients without any evidences of side effects (Park et al. 2019). In spite of abovementioned mechanisms in various studies, ginger as antiobesity agent enhances lipolysis and thermogenesis and suppression of lipogenesis as well (Ebrahimzadeh Attari et al. 2018). Thus, ginger and its constituents might be an alternative therapy for obesity and associated disorders.

1.8.12 Anti-Allergic Activity

Allergic disorders pose a significant burden on human health worldwide. Allergy refers to the development of immunological/hypersensitivity reactions to some allergens including pollens, perfumes, dust particles, mites, etc. resulting in tissue inflammation and organ dysfunction. Allergic mediators such as histamine and serotonin play a crucial role in allergy development by producing immunoglobulins especially IgE and T-cell populations (Kraithep et al. 2008; Thabet et al. 2018).

Ginger due to its anti-inflammatory activity has been widely studied against allergic disorders particularly rhinitis. *Zingiber officinale* capsules have shown anti-allergic effect in rhinitis patients by reducing total IgE level after 4 weeks of treatment course (Alsamarai et al. 2015). In another study, ginger (2%) and its bioactive constituent, namely, 6-gingerol, suppressed sneezing and infiltration of mast cells in nasal mucosa as well as secretion of IgE in ovalbumin-induced allergic rhinitis model. In addition, Th1 and Th2 cytokine expressions in OVA-sensitized cells were inhibited by 6-gingerol, thereby alleviating the symptoms of allergic rhinitis (Kawamoto et al. 2016). Recently, a randomized, double-blind, controlled clinical study on efficacy of ginger has shown notable decrease in total nasal symptom score (TNSS) and increase in the nasal cavity volume without side effects in allergic patients. However, the loratadine, standard drug, did not cause any change in the mentioned parameters (Yamprasert et al. 2020).

1.8.13 Antiviral Activity

Viral infections represent a major challenge for human population and affect three to five million people every year. Nowadays, influenza, AIDS, Ebola, and SARS (severe acute respiratory syndrome) are considered as the most serious viral infections. Classic antiviral agents mostly show minimal effectiveness owing to viral resistance and serious adverse effects, considering that researchers have earned a great attention from medicinal plants such as ginger to treat viral infections (Ben-Shabat et al. 2020; Denaro et al. 2020). Recent study has demonstrated that *Zingiber officinale* rhizome was effective against chikungunya virus. In this study, anti-chikungunya effect of ginger extract was monitored using Vero cell line followed by MTT assay. The experimental findings indicated an increase in cell viability by 51.05% and 35.10%, when the tested cultured cells were pre-treated with maximum non-toxic dose (MNTD) and half of MNTD of ginger extract, respectively (Kaushik et al. 2020). In addition, some previous studies on antiviral effect of ginger and its bioactive compounds have also been highlighted as can be seen in Table 1.12 (Dissanayake et al. 2020).

All the aforementioned studies clearly suggest the use of ginger and its phytochemicals against several kinds of viral infections.

1.8.14 Radioprotective

Individuals, who are regularly in contact with radiations of either natural or artificial, are more likely to be suffering from some kind of diseases. Excessive exposure to radiations may cause detrimental effects to body tissues particularly those who are working in nuclear centers and power plants and as astronauts and medical professionals. On the other hand, radiations can be used as beneficial tool for the treatment of human malignancies. In contrast, radiation therapy also has negative impact on normal cells and tissues around the tumor (Munteanu et al. 2015; Reisz

Table 1.12 Antiviral effects of various ginger extracts and constituents

Extract/part	Assay/cell lines	Results	Mechanism
Water extract	Plaque reduction assay in human upper (HEp-2) and low (A549) respiratory tract cell lines	Decreased plaque formation	Possibly due to secretion of IFN-β from mucosal cells Inhibited viral attachment and internalization
Lyophilized juice extract (5, 25, 50, 75, 100, 150, and 200 μg/mL)	Hepatocellular carcinoma HepG2 infected with hepatitis C virus	100 μg/mL dose was found effective against HCV-infected HepG2 cells	Inhibition of viral replication
Capsules of ethanolic extract (500 mg)	Egyptian HCV patients	Improved the altered viral load, α-fetoprotein, and liver functions	–
Aqueous extract	Feline calicivirus (FCV) as a surrogate for human norovirus	Inactivation of FCV	
Allicin		Anti-influenza effect against influenza A (H1N1)	Inhibition of neuraminidase (NA) protein responsible for initiation of infection
Ginger	Madin-Darby canine kidney (MDCK) cells	Inhibitory effect on MDCK cells	Production of TNF via macrophage activation Induction of TNF mRNA expression
Essential oil	Plaque reduction assay against herpes simplex virus type 2 (HSV-2) in vitro on RC-37 cells	Dose-dependent virucidal activity	

et al. 2014). Radioprotectors refer to the agents that protect the normal tissues against radiation-induced cell injury. In the present scenario, naturally occurring radioprotectives are being more preferred over available synthetic agent due to toxic effects at optimal concentration. Several preclinical investigations on experimental animals and in cultured cells have reported that ginger and its phytoconstituents, namely, zingerone and dehyrozingerone, are responsible for radioprotective activity (Baliga et al. 2012). In a study, hydroalcoholic extract has shown radioprotective effects in animals exposed to gamma radiations. The extract significantly inhibited lipid peroxidation and enhanced the level of GSH elevated by radiations. In addition, gastroprotective action was also shown by ginger extract (Jagetia et al. 2003). Furthermore, ginger oleoresin mitigates ionizing radiation-induced cytotoxicity, ROS production, and DNA strand breaks possibly through translocation of Nrf2 to cell nucleus and activation of cytoprotective gene expression

encoding for HO-1 and NQO-1 (Ji et al. 2017). Recent study has elaborated that oral administration of ginger extract (250 mg/kg) restored the level of 8-hydroxy-2-′-deoxyguanosine resulting in significant reduction in DNA oxidation in gamma ray radiation-induced genotoxicity in rats. In addition, chromosomal abnormality and micronucleus formation were lessened by ginger extract (Abd El-Monem and Elwakeel 2020). All together, ginger offers an immense radiotherapeutic potential against harmful radiations involving various mechanistic approaches such as free radical scavenging, antioxidant, anti-inflammatory, and anti-clastogenic effects (Baliga et al. 2012).

1.8.15 Anti-Thrombotic Effect

Interestingly, ginger and its phytochemicals have been documented to possess an effect on platelet aggregation in several animal models (Marx et al. 2015). It has been reported that oral dose of aqueous extract (500 mg/kg) caused significant reduction in the levels of serum PGE-2 and thromboxane-B 2 (Thomson et al. 2002). It has been shown in another study that combination of ginger and sappan wood extracts (56 mg:14 mg/20 g/day) extended the bleeding time and also prevented the paralysis in vivo against acute pulmonary thromboembolism model in mice (Saputri et al. 2017). Recent in vivo study performed on ginger methanolic extract has shown significant anti-thrombotic activity via inhibition of platelet aggregation (Shadrack et al. 2019). These results conclude that ginger might be a beneficial candidate for the treatment of thrombotic diseases.

1.9 Future Perspectives

Ginger has been considered as an interesting herbal remedy for the treatment of various diseases such as inflammation, constipation, indigestion, cold, diabetes, emesis, and pain. Despite vast research on chemical investigation and therapeutic effects of ginger, this herbal plant is getting more attention in the research domain to explore its unfolded pharmacological activities and phytochemistry. The aforementioned data explained about a plethora of phytochemicals and bioactivities of ginger and its corresponding derivatives. Nevertheless, future investigations require determining other pharmacological potentials of ginger extracts and its phytochemicals like gingerols, shogaol, etc. In addition, research should have concentrately focused on isolation, identification, and characterizations of some other phytoconstituents from ginger obtained from different geographical regions. Furthermore, ginger and its constituents require much more clinical trials in human beings to determine their safety, efficacy, and toxicological parameters.

1.10 Conclusion

In the current scenario, a broad range of diseases are becoming a global threat that affects the quality of individual's life. Unfortunately, synthetic medicines employed as preventive and treatment interventions are not adopted, since they are distinguished by serious side effects. Plant-based drugs are therefore used widely to treat these life-threatening diseases as safer therapeutic alternatives. Ginger (*Zingiber officinale*, Zingiberaceae), one of the popular and widespread dietary spices, is used for the treatment of several ailments. In addition, it is the main ingredient for many food products and nutraceuticals. This culinary spice acts as herbal remedy in various traditional medicine systems (Chinese, Indian, Iranian, and Unani) since long time. Ginger rhizome serves as storehouse for a wide range of bioactive phytochemicals including terpenes, phenolic compounds, proteins, carbohydrates, minerals, and many more. The volatile compounds of ginger are responsible for distinct aroma and flavor. Several researches have corroborated that ginger and its phytochemicals exhibit multiple bioactivities such as antioxidant, anti-inflammatory, antidiabetic, antiemetic, anticancer, cardioprotective, neuroprotective, antimicrobial, and other miscellaneous activities. In nutshell, ginger could be recommended as an excellent therapeutic candidate for the management of various health illnesses.

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2 An Insight into the Phytochemistry, Traditional Uses, and Pharmacology of *Ziziphus spina-christi* (L) Willd. *(Sidr)*: An Edible Wild Plant of Arabian Peninsula

U. M. Dhanalekshmi, Shah Alam Khan, Tanveer Alam, and Mubashir H. Masoodi

Abstract

Ziziphus spina-christi (L) Willd., belonging to the family Rhamnaceae, is a popular medicinal plant of Arabian peninsula. The plant being heat and drought resistant grows well in the extreme harsh environmental conditions of Middle East and North Africa (MENA) region. The ripe fruits are eaten as source of nourishment. The plant contains diverse classes of secondary plant metabolites such as cyclopeptide alkaloids, flavonoids, triterpenic acids, phenolic acids, tannins, volatile oils, fatty acids, saponins, etc.

Ziziphus spina-christi (*ZSC*) is used as a traditional medicine in Iran, India, Middle East, and several African countries. Almost all the parts of *ZSC* viz., the fruits, seeds, leaves, roots, and barks, are used by the herbalists and traditional medicinal practitioners for medicinal purpose to restore the good health. Many studies have shown the crude extracts of various parts of the *Ziziphus* plant to possess antimicrobial, anticancer, antidiabetic, antinociceptive, antihypertensive, antidiarrheal, and CNS effects. The outcomes of these scientific studies have by and large validated its folkloric uses. The plant owing to its high polyphenolic content has also been explored as an alternative source of biosynthesis of metal nanoparticles. Although *ZSC* fruits and leaves appear to be safe in experimental

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animals, there is a scarcity of the available scientific data on the toxicity associated with the consumption of the various parts of the *ZSC* plant.

This chapter aims to provide an updated comprehensive review of biologically active phytochemicals isolated from the various parts of the *ZSC*, traditional uses, patents granted, application in nanotechnology, and in vitro and in vivo pharmacological studies along with its toxicological profile.

Keywords

Ziziphus spina-christi · Christ's thorn · Cyclopeptide alkaloids · Traditional uses · *Sidr*

Abbreviations

5-HT	5-Hydroxyl tryptamine (serotonin)
ABTS	2,2-Azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) assay
AcOH	Acetic acid
AgNPs	Silver nanoparticles
ALKP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BALP	Bone alkaline phosphatase
BHT	Butylated hydroxytoluene
BMD	Bone mineral density
cAMP	Cyclic adenosine monophosphate
CCl_4	Carbon tetrachloride
CNS	Central nervous system
COVID	Coronavirus disease
sCT	Serum calcitonin
CuNPs	Copper nanoparticles
CV	Crystal violet
DA	Dopamine
DENA	Diethyl nitrosamine
DNA	Deoxyribonucleic acid
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EGFR	Epidermal growth factor receptor
FRAP	Ferric reducing/antioxidant power
GABA	Gamma-aminobutyric acid
GSH	Glutathione peroxidase
HbA1C	Hemoglobin A1c or glycated hemoglobin
HDL	High-density lipoproteins
HOMA	Homeostatic model assessment of β cell function
HOMA-IR	Homeostatic model assessment of insulin resistance

HORAC	Hydroxyl radical assay
HPLC-MS	High-performance liquid chromatography-mass spectrometry
HR	Heart rate
IGF-1	Insulin-like growth factor 1
IL-1β	Interleukin 1 beta
KATP	ATP-sensitive potassium channel
LD_{50}	Lethal dose in 50% of population
LDL	Low-density lipoproteins
LFT	Liver function tests
LPO	Lipid peroxidation
MCA	Metal chelation assay
MCH	Mean corpuscular hemoglobin
MDA	Malondialdehyde
MLZ	Mesalazine
MPP	1-methyl-4-phenylpyridinium
mRNA	Messenger ribonucleic acid
NE	Norepinephrine
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
OC	Osteocalcin
PC1	Procollagen type 1
PTH	Serum parathyroid hormone
PTZ	Pentylenetetrazol
qRT-PCR	Real-time quantitative reverse transcription Polymerase chain reaction
RFT	Renal function tests
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SC	Subcutaneous
SGOT	Serum glutamate oxaloacetate transferase
SGPT	Serum glutamate pyruvate transaminase
SMA	Spontaneous motor activity
SOD	Superoxide dismutase
SRSA	Superoxide radical scavenging activity
STZ	Streptozotocin
TRAP	Tartrate-resistant acid phosphatase
TRPA	Total reducing power ability
VLDL	Very-low-density lipoproteins
WHO	World Health Organization
ZSC	*Ziziphus spina-christi*
*ZSC*F	*Ziziphus spina-christi* fruits

2.1 Introduction

Ziziphus spina-christi (L) Willd., (*ZSC*) commonly known as Sidr in Arabic and Christ's thorn or Jujube in English belongs to the family Rhamnaceae. It is geographically distributed in a vast area of Africa, Asia, and Middle East (Motamedi et al. 2014). The species is native to several countries including Chad, Djibouti, Eritrea, Ethiopia, Kenya, Libya, Mali, Mauritania, Nigeria, Pakistan, Senegal, Somalia, Tunisia, Turkey, and Zimbabwe. The species is exotically distributed in Algeria, Comoros, Egypt, India, Iran, Iraq, Israel, Jordan, Madagascar, Morocco, Holland, Saudi Arabia, Syria, United Arab Emirates, and Zanzibar (Orwa et al. 2009).

It is known to be as one of the most heat-tolerating and drought-resistant fruit crops adapted to the harsh environmental conditions of Arabian Peninsula (Sudhersan and Hussain 2003). There are about 100 species in the genus *Ziziphus*, but among all *ZSC* is widely cultivated in Arabian Peninsula along with few other *Ziziphus* species for their edible fruits and wood. The tropical evergreen Sidr tree is approximately 10–12 m in height and grows widely throughout Oman but more prominently in Dhofar region and in Northern Oman during monsoon season. Its characteristic leaves which are ovate to elliptical in shape and are thinly hairy, glabrous beneath along the veins, distinguish it from other *Ziziphus* species (Miller and Morris 1988). Leaves are alternate, 2–4 cm long, 1.5–3 cm across, and have rounded tip with crenate or serrate margin, and the base is round to subcordate (Fig. 2.1). Although the nutritional value of *ZSC* leaves is not very high for domestic animals, in Northern Oman leaves are used as a source of livestock forage and fodder under open grazing field (Ghazanfar 1994a, b; Ghazanfar and Sabahi 1993).

The *ZSC* fruit is called *nabaq* and is rich in vitamin C. Since ancient time *ZSC* fruits are consumed by a large population in Oman villages as a source of nourishment. The fruit ripens during hot and dry weather, and the pulp of the yellow ripe fruit (diameter 1–1.5 cm) with a single obovate seed (6–7 × 5–6 mm, brown) tastes like apple. The fruit, if stored in dry place for long time, becomes reddish brown, sweeter, and softer with age (Miller and Morris 1988). The kernels are also eaten raw or cooked in water, milk, or buttermilk to treat the pneumonia. The fruits are eaten by grazing sheep and goats and the foliage by camels. The powdered sun-dried fruits are mixed with water to prepare cakes similar to gingerbread (Ali et al. 2006).

In Oman, the fruits are traditionally used for cleansing the stomach, purification of blood, and occasionally as abortifacient. The fruit has also been reported to stimulate appetite if eaten before meal and believed to possess anti-hair-falling properties. The *ZSC* leaves either crushed or chewed were used as cleansing agent for the whole body, particularly for hair and scalp as shampoo. The paste of the boiled leaves is used to treat headache, to soothe skin ulcers and infected sores, to reduce inflammation and pain of joints or fractured limbs. The decoction of leaves is said to have oxytocic properties and thus used to prolong the labor (Miller and Morris 1988; Ghazanfar 1994a, b).

Flowers are in dense clusters in the axil of the leaves. The calyx is five lobed and cup-shaped at the base and the petals are yellowish. The *ZSC* flowers are very

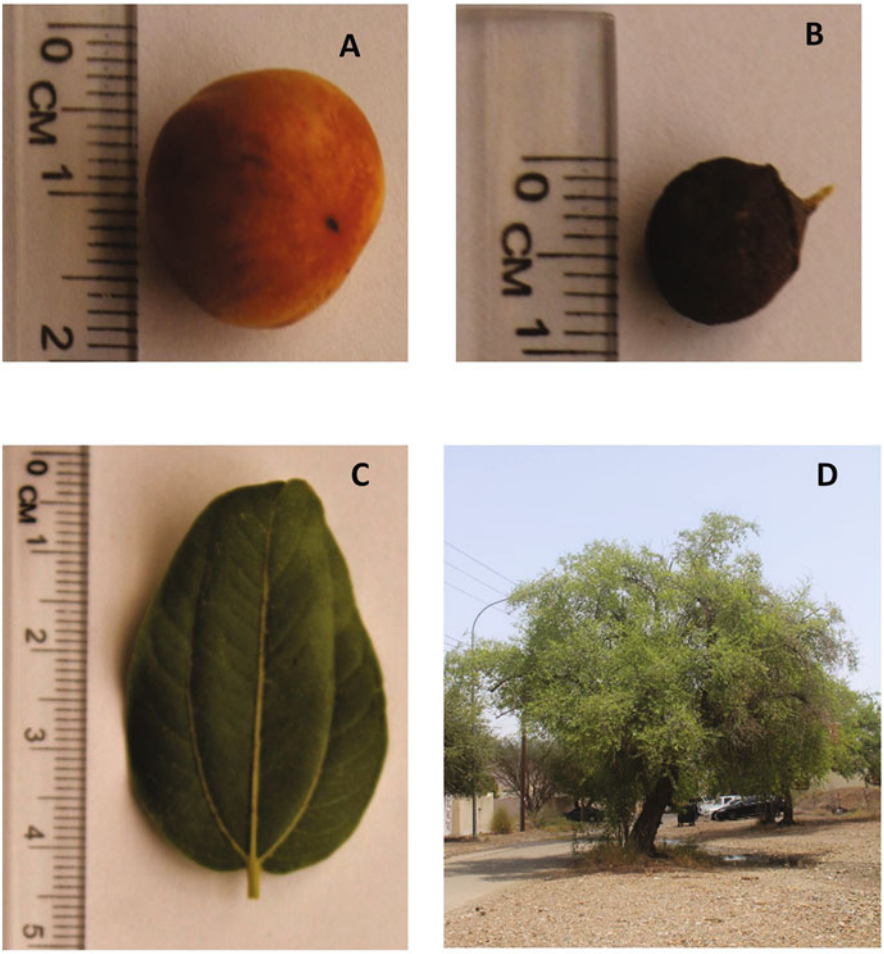


Fig. 2.1 Picture showing *ZSC* fruit (**a**), seed kernel (**b**), leaf (**c**), and full view of the tree (**d**). (Original pictures taken by Ms. Al Ghaliya Al Farsi, Oman)

important bee forage, and the honey produced there from is considered of excellent quality (Sudhersan et al. 2016).

2.2 Traditional/Folklore Medicinal Uses of *Ziziphus spina-christi*

ZSC has been traditionally utilized as a prominent medicine to uphold health (El Ghazali et al. 1994). Majority of the folklore claims of *ZSC* are scientifically validated and reported, but some traditional uses are prevalent in one or other cultural groups/regions. As per the WHO report, majority of the people from the

developing countries still rely on traditional cures prepared from natural sources for their primary healthcare needs. A large number of people especially in areas that have difficulty to access modern pharmaceuticals completely depend on traditional uses of natural medicine for acute and chronic ailments (Carmona and Pereira 2013). Various parts of the *Ziziphus* plant including crude extracts of root, stem, flower, fruit, and twigs have been extensively explored for the diverse pharmacological activities in order to validate its folklore claim. The results of several in vitro and in vivo pharmacological studies have validated and supported the ethnopharmacological uses of *ZSC* and are presented in Table 2.1.

ZSC is a very popular traditional medicine in Iran, India, Middle East, and several African countries. Almost all the parts of *ZSC*, viz., the fruits, seeds, leaves, roots, and bark, are used for medicinal purpose to maintain and restore good health (Asgarpanah and Haghighat 2012).

In India, a formulation prepared using *ZSC* bark is used for the cleansing of wounds and sores. The gum of the tree is used to treat eye diseases, while the leaves are chewed to mask the bitter or unpleasant taste of medicines (Miller and Morris 1988). A narcotic beverage made from the fruits is used as tranquilizer and sedative in Egypt and the southern Sahara (Younes et al. 1996). Egyptian use leaves along with the conventional medicines to treat abscesses, bubbles, and swollen eyes. The fiery wood debris is applied topically to treat snakebite (Abdel-Galil and El-Jissry 1991).

In Saudi Arabia, the fruits are eaten for their laxative property, and the leaves are used to heal wounds, to treat skin diseases, as diuretic, and also as a body wash. The stem bark is used in toothache and as an antipyretic (Tanira et al. 1988; Ali et al. 2006). In Morocco, the fruits are used for their emollient and astringent actions, while the leaves are used to reduce eye inflammation (Ali et al. 2006).

In Sudan, the sore throat is treated by eating fruits, the bark is used for chest pain, and a root infusion is taken orally to combat dysentery (El Ghazali et al. 1997). The roots are popularly used in the treatment of urinary and gynecological problems in Zimbabwe. Bark decoctions have been reported to be used for chest diseases in South Africa. In Mali and Niger, the roots and the leaves are utilized for gastric infections, chest pain, sexually transmitted diseases, diarrhea, wounds, constipation, and nervousness (El Ghazali et al. 1997; El Maaiden et al. 2020).

2.3 Phytochemistry of *ZSC*

The phytochemistry and related aspects of all the parts of *ZSC* plant have been extensively studied over the past five to six decades. The phytochemical analysis has resulted in the isolation, separation, and identification of hundreds of minor and major phytoconstituents of diverse chemical classes (Fig. 2.2). *ZSC* is reported to contain cyclopeptide alkaloids, flavonoids, triterpenic acids, phenolic acids, tannins, volatile oils, fatty acids, saponins, etc. However, maximum numbers of compounds have been isolated from the *ZSC* leaves (Fig. 2.3).

Table 2.1 Traditional pharmacological uses of various parts of *ZSC*

Plant parts	Traditional pharmacological uses	References
Leaf	Chest pains, asthma, headache, eye inflammations, diarrhea, stomach pain, constipation, hemorrhoids, anthelmintic, increase milk production, ease prolonged labor, blisters, skin diseases and disorders, abscesses and furuncles, lung-related problems, chest and pectoral problems, blood purifier and tonic, high blood pressure, fractures, emollient, cooling, tonic, stomachic, astringent, hair problems, infant's powder, nervousness, numb the taste buds, insomnia, antidiabetic, gonorrhea, sex diseases, inflammatory conditions, ulcers, wound healing, heartburn	Miller and Morris (1988), Dafni et al. (2005), Saied et al. (2008), Ads et al. (2017), Abdel-Zaher et al. (2005), Abdel-Galil and El-Jissry (1991), Kadioglu et al. (2016), Panche et al. (2016), Dkhil et al. (2018a, b), Dafni et al. (2005), Bown (1995), Neuwinger (1996), Iwu (1993), Asgarpanah and Haghighat (2012) and Deshpande et al. (2019)
Root	Toothache, gum problems, arthritis, general painkiller, eye inflammations, antipurgative	El Ghazali et al. (1994), Dafni et al. (2005), Saied et al. (2008), Abdel-Galil and El-Jissry (1991) and Neuwinger (1996)
Bark	Toothache, gum problems, anodyne, cooling, tonic stomachache, intestinal spasms, body rinse, to cure fresh wounds	El Ghazali et al. (1994), Dafni et al. (2005), Saied et al. (2008) and Abdel-Galil and El-Jissry (1991)
Stem	Nervousness, heart pains, muscle pains, scorpion sting, rheumatism, anti-inflammatory for eye wash, treat toothache and stomachache, antirheumatic, dysentery, bronchitis, coughs, and tuberculosis	El Kamali and El Khalifa (1999), Ali-Shtayeh et al. (1998), Dafni et al. (2005), Saied et al. (2008), Ads et al. (2017), Alzahrani et al. (2016), Panche et al. (2016) and Dkhil et al. (2018a, b)
Fruit	Anus problems, liver problems, swollen organs, weight reduction, colds, febrifuge, measles, stomachache, cooling, depurative, plood purifier and tonic, lung, chest, and pectoral problems, burns, blisters, wounds, promoting pregnancy, diarrhea, anthelmintic, stomach disorders, aches, constipation, heartburn, headache, chest pains, asthma, bruises, dysentery, bronchitis, coughs, tuberculosis	Jongbloed (2003), Dafni et al. (2005), Saied et al. (2008), Ads et al. (2017), Alzahrani et al. (2016), Abdel-Galil and El-Jissry (1991), Kadioglu et al. (2016), Panche et al. (2016), Neuwinger (1996), Guizani et al. (2013), Deshpande et al. (2019) and Asgarpanah and Haghighat (2012)
Seed	Hair problems, blisters, anthelmintic, eye inflammations, headache, chest pains, asthma, bruises	Dafni et al. (2005), Saied et al. (2008), Abdel-Galil and El-Jissry (1991), Dkhil et al. (2018a, b) and Asgarpanah and Haghighat (2012)
Wood	Toothache, gum problems	Dafni et al. (2005) and Saied et al. (2008)
Resin	Hair problems, febrifuge, skin diseases	Dafni et al. (2005) and Saied et al. (2008)

Fig. 2.2 Various chemical classes of phytochemicals identified in *ZSC*

2.3.1 Volatile Oils in the Leaves, Fruits, and Flowers of *ZSC*

The major volatile constituents of the leaves of *ZSC* grown in Iran were identified as geranyl acetone (14.1%) and farnesyl acetone C (9.9%). The minor volatile constituents of the *ZSC* leaves include β-eudesmol (3.8%), *E*-β-ionone (1.4%), spathulenol (1.2%), terpinolene (1.2%), germacrene D (1.1%), and nerolidol (1.1%). *Allo*-aromadendrene, β-pinene, β-caryophyllene, α-terpineol, α-pinene, 1,8-cineole, nerol, aromadendrene, δ-cadinene, *p*-cymene, and limonene were also detected in the oil, but their concentration was found to be less than 1% (Ghannadi et al. 2003). However, another study carried out by Fard et al. using the aerial parts of *aucheri* variety of *ZSC* grown in the same region of Iran could only identify 11 compounds representing 92.14% of the volatile oil. They identified carotol (42.20%) as the main constituent (Fard et al. 2020). On the other hand, the leaves

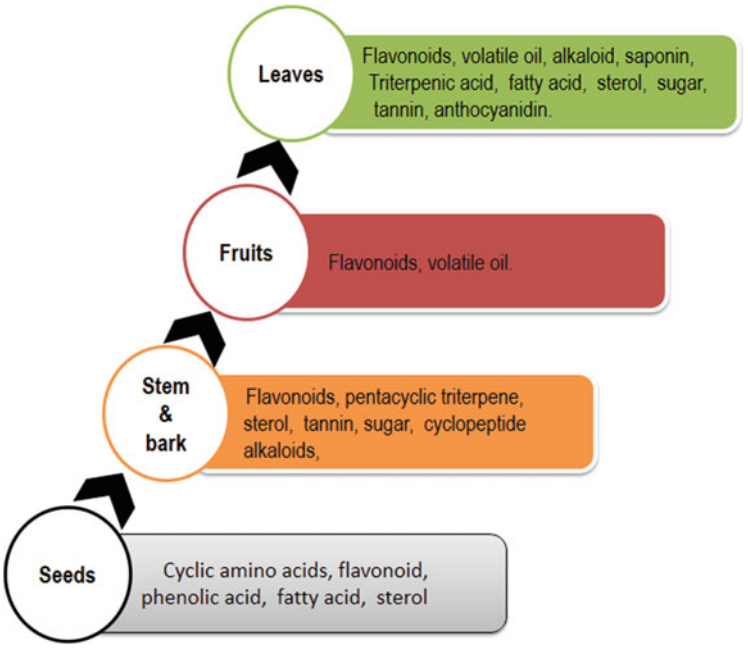


Fig. 2.3 Major chemical classes of phytochemicals present in different parts of *ZSC*

of the Egyptian variety have been reported to be rich in α-terpineol (16.4%) and linalool (11.5%) (Younes et al. 1996).

The chemical composition of volatile oil isolated from the fresh fruits of *ZSC* grown in Giza, Egypt, was reported by Said et al. (2010a, b). The GC-MS analysis revealed the presence of 21 chemical compounds in the fresh fruits constituting 99.3% of the oil. The major constituents of the oil were found to be dodecanoic acid (22.4%) and oleic acid methyl ester (17.1%) (Said et al. 2010a, b).

Flower volatile constituents of *ZSC* collected from Alexandria, Egypt, were isolated using closed-loop stripping analysis (CLSA) and solid-phase micro-extraction (SPME) techniques. The oil upon GC-MS analysis showed the presence of 22 volatile compounds belonging to different chemical classes, viz., aldehyde (19.69%), monoterpene-alcohol (22.78%), ketone (18.12%), ester (3.80%), and hydrocarbon (21.64%). Linalool (16.34%) was characterized as the major constituent, but nonanal (11.56%), D-limonene (6.43%), lavandulol (2.59%), and α-terpineol (0.96%) were also identified in the floral oil. The flowery, fruit, and sweet smell odors of the characterized volatile constituents were attributed to the characteristic unique odor of the flowers of *ZSC* (Shonouda et al. 2008). The chemical structures of some identified volatile constituents in the *ZSC* are presented in Fig. 2.4.

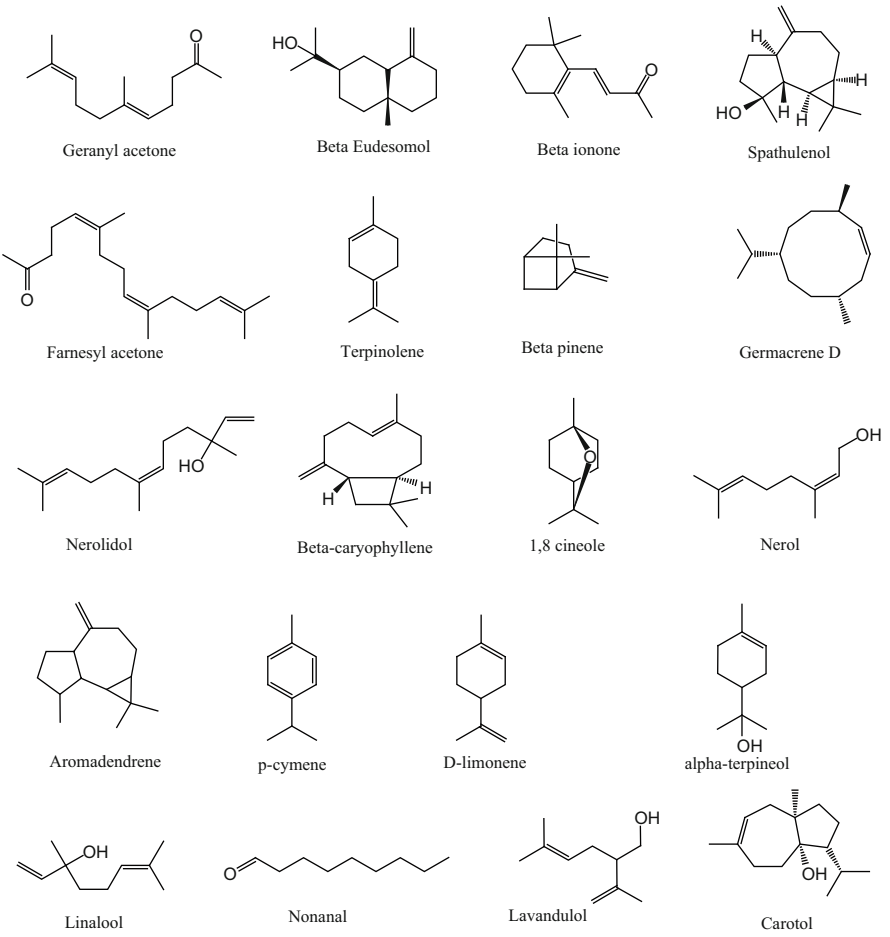


Fig. 2.4 Chemical structures of some important chemical constituents present in the *ZSC* volatile oil

2.3.2 Phytochemicals Isolated from the Leaves of *ZSC*

Phytochemical investigations of the leaves of *ZSC* have shown the presence of various chemical classes of secondary plant metabolites. However, the yield and extraction efficiency of biologically active secondary metabolites from the *ZSC* leaves depend upon the polarity of solvents. Leaves of *ZSC* are widely used by traditional medical practitioners/herbalists in the gulf region for the treatment of skin diseases and to heal wounds. The leaves are also used as anti-inflammatory, antipyretic, and diuretic and as a body wash. The chemical compounds characterized in the various organic extracts of *ZSC* leaves are presented in Table 2.2 which indicates that leaves predominantly contain flavonoid glycosides, cyclopeptide alkaloids, saponins, and triterpenic acid besides lipids, volatile oils, and carbohydrates. The

Table 2.2 Chemical compounds isolated from the *ZSC* leaves extract

S. no.	Chemical class	Name of chemical compound	Reference
1.	*C*-flavonoid glycoside	Naringenin-6,8-dihexoside	Okamura et al. (1981)
2.		(*Epi*)catechin-di-*C*-hexoside	Pawlowska et al. (2009)
3.		3′,5′-Di-*C*- β-D-glucosylphloretin	Nawwar et al. (1984)
4		Apigenin-6-*C*-glucoside	Nawwar et al. (1984)
5.	*O*-flavonoid glycoside	Myrecetin-3-*O*-(6-rhamnosyl) hexoside-*O*-glycoside	Sakna et al. (2019)
6.		Quercetin-3-*O*-(2,6-dirhamnosyl) hexoside	Bozicevic et al. (2017)
7.		Quercetin-3-*O*-(2,hexosyl)-6-rhamnosyl) hexoside	Sakna et al. (2019)
8.		Kaempferol-3-*O*-(2,6-dirhamnosyl) hexoside	Pawlowska et al. (2009)
9.		Quercetin-3-*O*-robinoside	Pawlowska et al. (2009)
10.		Quercetin-3-*O*-rutinoside	Pawlowska et al. (2009)
11.		Bayarin	Devkota et al. (2013)
12.		Quercetin-3-*O*-hexoside	Devkota et al. (2013)
13.		Kaempferol-3-*O*-rutinoside	Devkota et al. (2013)
14.		Quercetin-3-*O*-(2-pentosyl-rhamnoside)-4′-*O*-rhamnoside	Devkota et al. (2013)
15.		Taxifolin-3-*O*-glucoside	Ali et al. (1984)
16.		Apigenin-7-*O*-glucoside	Nawwar et al. (1984)
17.		Quercetin-3-*O*-glucoside-7-*O*-rhamnoside	Nawwar et al. (1984)
18.	*Acyl*-flavonoid glycoside	Quercetin-3-*O*-*p*-coumaroyl (2,6-dirhamnosyl)-hexoside	Sakna et al. (2019)
19.		6′″-Caffeoyl 3′,5′-di-C-glucopyranosylphloretin	Sakna et al. (2019)
20.		Quercetin-3-*O*-(4-*O*-*p*-coumaroyl)-2-rhamnosyl-[6-rhamnosyl]-galactoside (16)	Bozicevic et al. (2017)
21.		Kaempferol-3-*O*-(4-*O*-*p*-coumaroyl)-2-rhamnosyl-[6-rhamnosyl]-galactoside	Sakna et al. (2019)
22.		Quercetin-3-*O*-(4-*O*-*p*-coumaroyl)-2-rhamnosyl-[6-rhamnosyl]-glucoside	Sakna et al. (2019)
23.	Flavonoid Alkaloid	Taxifolin	Ali et al. 1984
24.		Dihydrokaempferol	Ali et al. (1984)
25.		Rutin	Nawwar et al. (1984)
26.		Hyperin	Nawwar et al. (1984)
27.		Quercetin	Nawwar et al. (1984)
28.		Mauritine F	Gournelis et al. (1998)
29.		Daechuine S5	Gournelis et al. (1998)
30.		4(13)-Nummularine-C	Sakna et al. (2019)
31.		Sanjoinine B	Gournelis et al. (1998)

(continued)

Table 2.2 (continued)

S. no.	Chemical class	Name of chemical compound	Reference
32.		Oxyphylline A	Tuenter et al. (2017a, b)
33.		Lotusanine A/Frangufoline	Gournelis et al. (1998)
34.		Jubanine C	Tripathi et al. (2001)
35.		Adouetine Z	Gournelis et al. (1998)
36.		Scutianine-A	Gournelis et al. (1998)
37.	Saponin	Jujubogenin-3-*O*-(di-deoxyhexosyl)-hexoside	Sakna et al. (2019)
38.		Jujuboside B1	Matsuda et al. (1999)
39.		Christinin A–D	Mahran et al. (1996)
40.		Christinin A1 and A2	Bozicevic et al. (2017)
41.		15-acetoxy lotoside IV	Bozicevic et al. (2017)
42.		Jujubasaponin II/III isomer	Yoshikawa et al. (1992)
43.		Jujubogenin	Kamil et al. (2000)
44.		Lotoside III	Bozicevic et al. (2017)
45.		Siconigenin-3-*O*-α-L-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranoside	Bozicevic et al. (2017)
46.		Konarigenin-3-*O*-α-L-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranoside	Bozicevic et al. (2017)
47.		Onigenin-3-*O*-α-L-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranoside	Bozicevic et al. (2017)
48.	Triterpenic acid	Oleanonic acid	Guo et al. (2011)
49.		Ceanothic acid	Ikram and Tomlinson (1976)
50.		Alphitolic/maslinic acid	Bai et al. (2016)
51.		Zizyberanalic acid/pomonic acid	Guo et al. (2011)
52.		Ceanothic acid isomer	Guo et al. (2010) and Leal et al. (2010)
53.		3-*O*-*Z*-*p*-Coumaroylalphitolic acid/3-*O*-*Z*-*p*-coumaroylmaslinic acid	Guo et al. (2011)
54.		Betulinic acid	Ikram and Tomlinson (1976) and Ali et al. (1984)
55.		Ursolic acid	Ali et al. (1984)
56.	Fatty acid	Trihydroxy-octadecadienoic acid	Sakna et al. (2019)
57.		Dihydroxy dodecadienoic acid	Sakna et al. (2019)
58.		Trihydroxy-octadecenoic acid	Sakna et al. (2019)
59.		Amino-hexadecanediol	Sakna et al. (2019)
60.		Amino-methyl; heptadecanetriol	Sakna et al. (2019)
61.		2-Amino-1,3-octadecanediol	Sakna et al. (2019)
62.		Octadecatetraenoic acid	Sakna et al. (2019)

(continued)

Table 2.2 (continued)

S. no.	Chemical class	Name of chemical compound	Reference
63.		Myristic acid	Ali et al. (1984)
64.		Stearic acid	Ali et al. (1984)
65.		Oleic acid	Ali et al. (1984)
66.		Linoleic acid	Ali et al. (1984)
67.		Arachidic acid	Ali et al. (1984)
68.		Cetyl alcohol	Ali et al. (1984)
69.	Steroid/sterol	β-Sitosterol	Ali et al. (1984)
70.		Sitosterol β-D-glucoside	Weinges and Schick (1995)
71.	Sugar	Lactose, glucose, galactose, arabinose, sucrose, xylose, and rhamnose	Brantner and Males (1999) and Weinges and Schick (1995)
72.	Tannin	(+)-Gallocatechin (1.7%)	Weinges and Schick (1995)
73.		(−)-Epigallocatechin (0.9%)	Weinges and Schick (1995)
74.	Anthocyanidin	Dodecaacetylprodelphinidin B3	Weinges and Schick (1995)
75.		Polymers of prodelphinidins	Weinges and Schick (1995)

flavonoid content (145 mg/g) of dried extract of *ZSC* leaves is quite higher than the alkaloid (10.1 mg/g) or tannin contents (17.7 mg/g) (Khaleel 2018a). The traditional uses of leaves of *ZSC* could be attributed to the presence of large number of bioactive compounds. Several scientific studies have been conducted to validate the pharmacological properties of the characterized compounds in the leaves (Tanira et al. 1988; Glombitza et al. 1994). Christinin A, the principle saponin glycoside of leaves of *ZSC*, has been shown to exert hypoglycemic effect in diabetic rats (Glombitza et al. 1994). Presence of saponins in the leaves imparts good surface activity making it a good detergent even at low concentration. This justifies the folkloric use of aqueous extract of leaves as a natural shampoo in Oman and other gulf countries. A pure herbal shampoo formulated using aqueous *ZSC* leaves extract showed comparable results with the branded commercial shampoo available in the market in terms of cleansing, detergency, surface tension, bubble size, foam stability, % solid content, and conditioning performance (Al-Badi and Khan 2014).

Weinges and Schick detected dodecaacetylprodelphinidin B3, a proanthocyanidin from the dried leaves of *ZSC*. They also identified the presence of sugars [glucose (4.4%), sucrose (21%), oligomers and polymers of prodelphinidins (16%), betulinic acid (1.7%), sitosterol β-D-glucoside (2%), and tannins (+)-gallocatechin (1.7%) and (−)-epigallocatechin (0.9%)] in the butanol extract of the leaves (Weinges and Schick 1995). Bozicevic et al. (2017) characterized 10 dammarane-type saponins and 12 known phenolic compounds

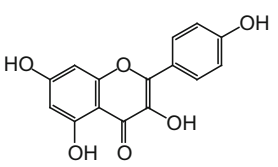
from the *ZSC* leaves. Eight saponins were isolated for the first time from *ZSC* leaves (Bozicevic et al. 2017). The list of chemical compounds isolated from the leaves of *ZSC* is presented in Table 2.2, and structures are given in Fig. 2.5.

2.3.3 Phytochemicals Isolated from the Stem, Root, and Barks of *ZSC*

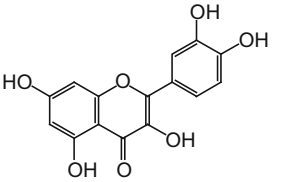
The phytochemical investigation of *ZSC* stem bark revealed the presence of a novel bioactive class of polyamidic compounds classified as cyclopeptide alkaloids (Tschesche et al. 1974; Shah et al. 1986; Abdel-Galil and El-Jissry 1991). Cyclopeptide alkaloids are made up of two parts, a 13-, 14-, or 15-membered macrocyclic ring and a side chain. Majority of these alkaloids contain a 14-membered ring, but few compounds with a 13-membered ring, e.g., amphibine-H, jubanine-A, and zizyphine-F belonging to zizyphine-A type, were also characterized. Cyclopeptide alkaloids with 14-membered rings are frangulanine-type compounds (with a β-hydroxyleucine moiety), amphibine-B/D/F-type compounds (with a β-hydroxyproline), and integerrine-type (with a β-hydroxyphenylalanine) moieties. Nummularine-D and Nummularine-E are examples of integerrine type of alkaloids. Occurrence of spinanine-A, B, and C, 14-membered cyclopeptide alkaloid of the amphibine-B type, has been reported in the bark (Tuenter et al. 2017a, b; Fathy et al. 1990). Some more cyclic peptide alkaloids such as franaganine, mauritine C, and sativanine A were also isolated from the stem bark of *ZSC* (Tschesche et al. 1974; Shah et al. 1986). Soliman et al. identified 13-dehydrobetulin [(EtOH) λ_{max} 210 nm)], a novel betulin derivative from *ZSC* stems (Soliman et al. 2019). Mohammed et al. demonstrated the anticholinergic properties of the ethanolic extracts of stem bark of *ZSC* and provided the scientific evidence that the plant's folkloric use as antispasmodic is partly or wholly due to the presence of bioactive cyclopeptide alkaloids (Mohammed et al. 2012).

A pentacyclic triterpene exhibiting antiplasmodial activity was isolated from the *ZSC* root bark. The bioactive compound was characterized as betulinic acid (also known as mairin) (Adzu et al. 2011).The organic extracts of various polarities of stem bark of *ZSC* have yielded betulin, hexadecanoic acid ethyl ester, and phytol in major amounts, while quercetin (0.46%), stigmasterol (0.65%), and α- sitosterol (0.68%) were detected in minor quantities (Ads et al. 2018). The bark contains condensed tannins (9.25%) as well as leucocyanidin (Singh et al. 1965). Free sugars such as fructose, glucose, raffinose, and sucrose have also been identified (Ghazanfar 1994a, b). Presence of epigallocatechin and gallocatechin in the *ZSC* stem extract is also documented (Kadioglu et al. 2016). Lupeol and betulinaldehyde, two lupane-type triterpenoids, and β-sitosterol, a sterol, were isolated for the first time from the root bark of *ZSC* grown in Sudan (Elnagar and Modawi 2016).

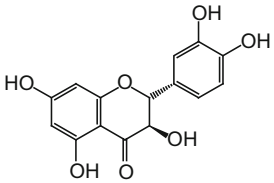
The ethanolic extract of *ZSC* roots furnished a flavonoid epicatechin which exhibited potent antioxidant and insecticidal activity (Elaoui et al. 2020). The chemical structures of some major phytochemicals isolated from the stem, root, and barks of *ZSC* are given in Fig. 2.6.



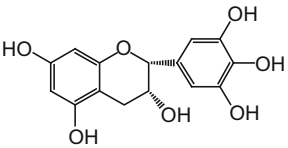
Kaempferol



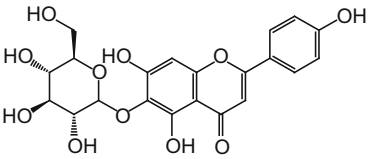
Quercetin



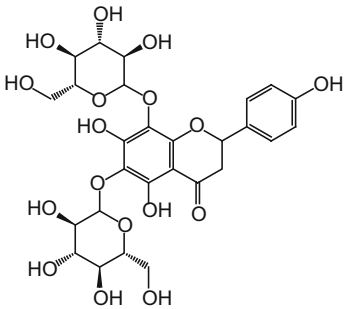
Taxifolin



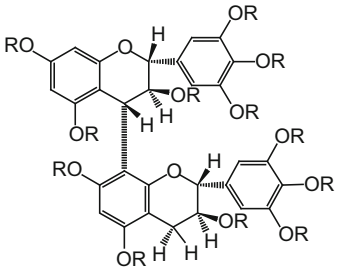
Epigallocatechin



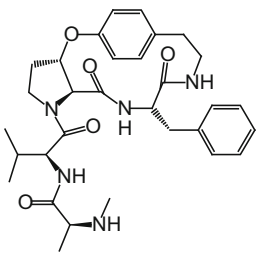
Apigenin-6- C-glucoside



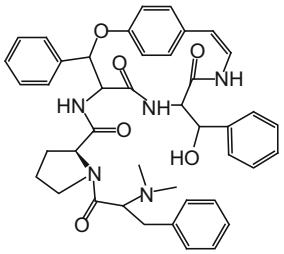
Naringenin 6,8 dihexoside



R=H=Procyanidine
R=$COCH_3$= decaacetylprocyanidine

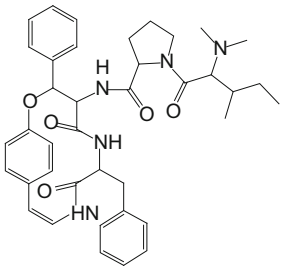


Mauritine F

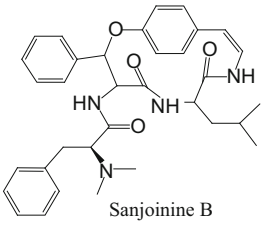


Oxyphylline A

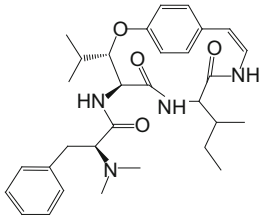
Fig. 2.5 Chemical structures of some important and major chemical constituents isolated from *ZSC* leaves



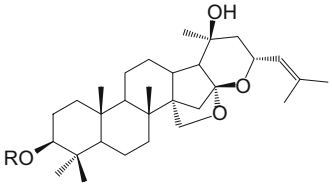
Jubanine C



Sanjoinine B

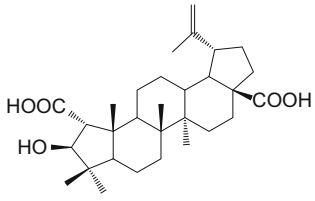


Lotusanine A

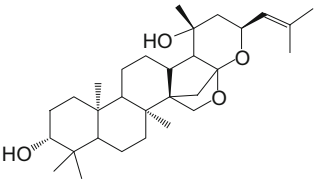


Christinin A R= [Fru-(1→2)]-[Glu-(13)]-Ara

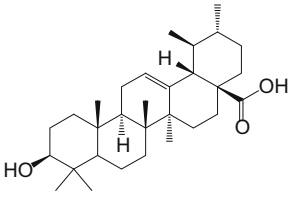
Christinin A R= [Glu-(1→2)]-[Rha-(13)]-Ara



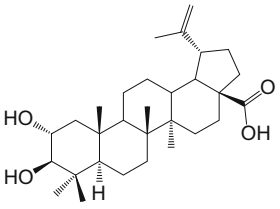
Ceanothic acid



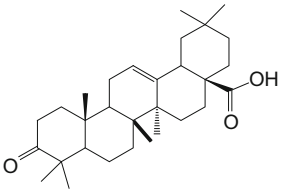
Jujubogenin



Ursolic acid



Alphitolic acid



Oleanonic acid

Fig. 2.5 (continued)

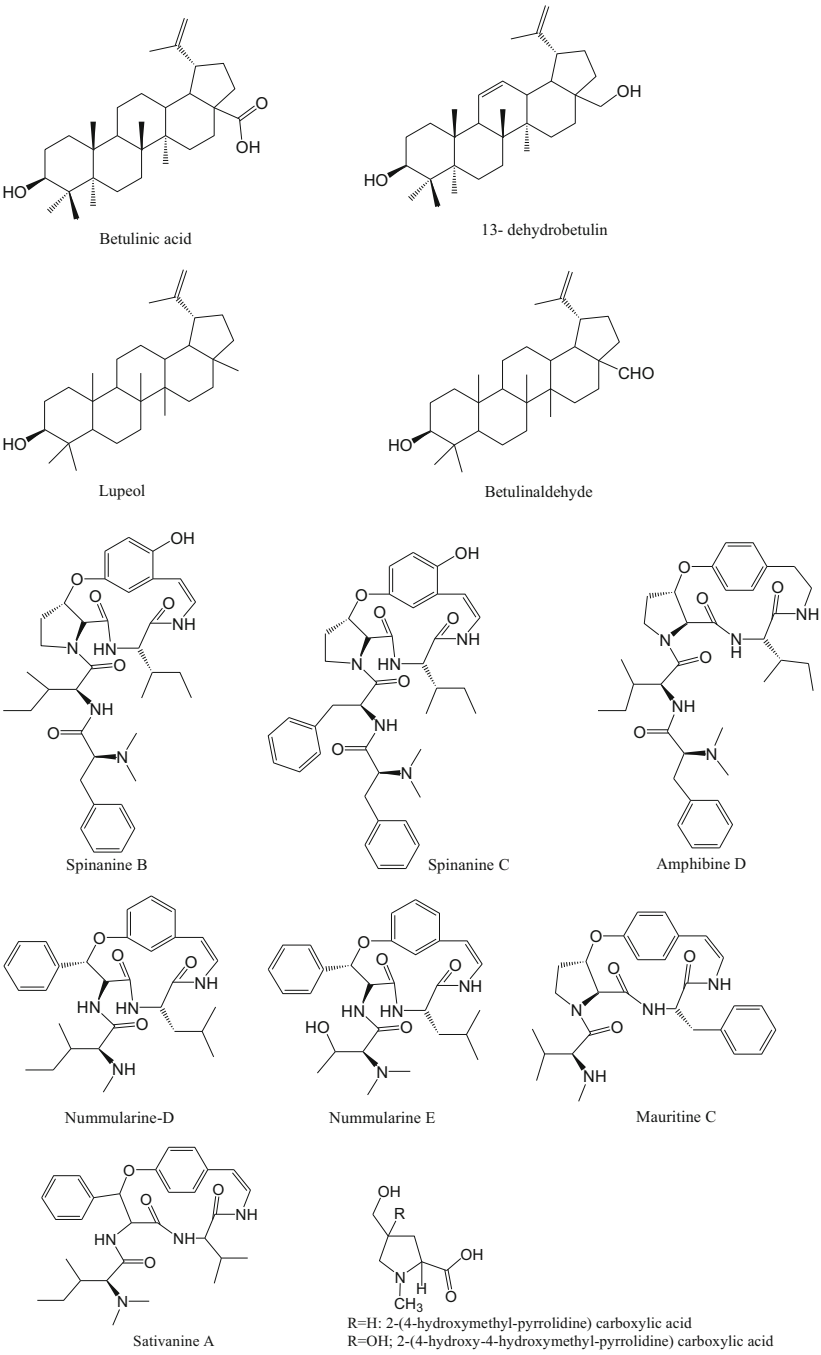


Fig. 2.6 Chemical structures of some important chemical constituents present in the *ZSC* stem, root, and bark

2.3.4 Phytochemicals Isolated from the Fruits of *ZSC*

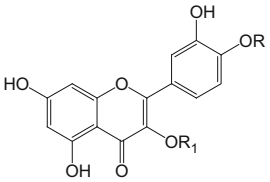
The edible part of *ZSC* fruits without seeds (pulp) is a good source of carbohydrates (85.69%). It contains free sugars [glucose (6.2%), rhamnose (2.6%), xylose (5.7%), and fructose (78%) of total sugars] and 7.5% of mucilage content making it a popular demulcent and emollient in the traditional medicine (Nazif 2002; Ads et al. 2017). Berry-Koch et al. reported that approximately 4.8 g protein, 0.9 g fat, 3.7 mg niacin, and 30 mg ascorbic are present in 100 g of the dried fruit pulp giving approximately 315 calories (Berry-Koch et al. 1990), while the content of protein and fat in Sudanese *ZSC* fruit pulp was found to be 4.56 and 1.17 g (Osman and Ahmed 2009).

Shahat et al. (2001) reported the isolation of the flavonoids quercetin, hyperoside, and rutin and a novel flavonol triglycoside quercetin-3-*O*-[β-xylosyl-(1 → 2)-α-rhamnoside] 4′-*O*-α- rhamnoside) from the ethylacetate fraction of the ethanolic extract of *ZSC* fruits (Shahat et al. 2001). The extract also exhibited significant antiviral activity against *Herpes simplex type 1* (HSV1). Pawlowska et al. (2009) isolated ten flavonoid glycosides of O and C types from the methanol extract of ripe edible fruits of *ZSC*. The glycosylated flavonoids were having quercetin and kaempferol aglycones connected to one, two, or three sugar moieties. One C-glycoside, 3′,5′-di-C-β-D-glucosylphloretin, was also detected by means of HPLC/ESI-MS analyses. The identified flavonoids include quercetin 3-*O*-robinobioside, quercetin 3-*O*-rutinoside, kaempferol 3-*O*-robinobioside, kaempferol 3-*O*-rutinoside, quercetin 3-*O*-α-L-arabinosyl-(1 → 2)-α-L-rhamnoside, quercetin 3-*O*-β-D-xylosyl-(1 → 2)-α-L-rhamnoside, quercetin 3-*O*-β-D-galactoside, quercetin 3-*O*-β-D-glucoside, and quercetin 3-*O*-β-D-xylosyl-(1 → 2)-α-L-rhamnoside-4′-*O*-α-L-rhamnoside (Pawlowska et al. 2009) (Fig. 2.7). Phenolic compounds such as *p*-hydroxybenzoic acid, tyrosol, vanillic acid, caffeic acid, gallic acid, *p*-coumaric acid, tannic acid, ferulic acid, etc. have been isolated from the fruits of *ZSC* (Amany et al. 2013).

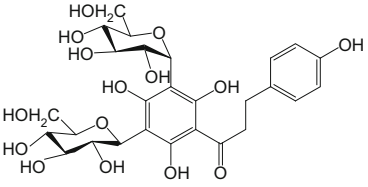
GC-MS analysis of nonpolar (n-hexane) extract of *ZSC* fruits led to the identification of 26 chemical compounds comprising of aromatic hydrocarbons and volatile compounds. The main aromatic hydrocarbons identified in the extracts were 6-phenyl-dodecane (14.90%); 6-phenyl-tridecane (11.38%); 2, 3, 4, and 5-phenyl-undecane (30.65%); and 2, 3, and 4-dodecane (15.67%). Some of the identified volatile constituents include m-cymene (1.95%), crypton (1.58%), α-pinene (1.20%), (+)-sabinene (1.11%), α-bergamotene (0.56%), and farnesan (0.47%) (El-Hefny et al. 2018).

2.3.5 Phytochemicals Isolated from the Seeds of *ZSC*

The total protein content and total lipid content of *ZSC* seeds were reported to be 15.9% and 2.3% of dry weight. Seeds showed the presence of 15 amino acids out of which 70% were non-essential and 17.1% semi-essential and essential amino acids made up only 12.8% of the total mixture (Hashem and Saleh 1999). Saponifiable fraction showed the presence of 13 fatty acids comprising of 83.5% unsaturated and



R	R_1	Chemical name
H	rha-(1→6)-gal	Quercetin 3-O-robinobioside
H	rha-(1→6)-glc	Quercetin 3-O-rutinoside
H	ara-(1→2)-rha	Quercetin 3-O-α-L-arabinosyl-(1→2)-α-L-rhamnoside
H	xyl-(1→2)-rha	Quercetin 3-O-β-D-xylosyl-(1→2)-α-L-rhamnoside
rha	xyl-(1→2)-rha	Quercetin 3-O-β-D-xylosyl-(1→2)-α-L-rhamnoside-4'-O-α-L-rhamnoside



3',5'-di-C-β-D-Glucosylphloretin

Fig. 2.7 Chemical structures of some major chemical constituents present in the *ZSC* fruits and seeds

16.5% saturated acids. Linoleic acid C18:2 (45%) and linolenic acid C18:3 (20.01%) were noted to be the major fatty acids. Hasham and Saleh suggested that the broad-spectrum antimicrobial activity of the plant extracts might be due to their high content of unsaturated fatty acids (Hashem and Saleh 1999). Unsaponifiable fraction contained a mixture of n-C12 to n-C30 hydrocarbons with hexacosane (n-C26) being the major component (12.9% of total unsaponifiable matter). Cholesterol and β-sitosterol were also detected in significant amounts of 21.7% and 27.1%, respectively (Nazif 2002).

Said et al. reported the isolation and characterization of two new cyclic amino acids, 4-hydroxymethyl-1-methyl pyrrolidine-2-carboxylic acid and 4-hydroxy-4-hydroxymethyl-1-methyl pyrrolidine-2-carboxylic acid (Said et al. 2010a, b), and three phenolic compounds (*p*-hydroxybenzoic acid, kaempferol, and rutin from the methanolic seeds extract of *ZSC* (Said et al. 2011). The HPLC-MS profiling of *ZSC* methanolic seed extract leads to the characterization of spinosin, 6‴ sinapoylspinosin, and 6‴ feruloylspinosin. These flavonoids have been known to act on the GABA and serotonin systems in CNS and produce anxiolytic, memory-ameliorating, and sleep-inducing effects. The flavonoids constituted 15.2%, 4.6%, and 9.7% of the total extract, respectively (Kadioglu et al. 2016; Wang et al. 2010; Liu et al. 2014). Proximate analysis of *ZSC* seed kernels (on dry weight basis) showed the presence of moisture (4.22%), crude protein (38.2%), crude fat

(30.19%), and carbohydrate (28.1%). The seed kernels were found to contain potassium (365.01 mg/100 g of dry sample), phosphorus (87.71 mg), sodium (24.96 mg), iron (4.21 mg), zinc (4.35 mg), copper (2.94 mg), and traces of manganese. The *ZSC* kernel oil contains 79.2% total unsaturated fatty acids and 20.8% total saturated fatty acids. Palmitic acid (C16:0) and stearic acid (C18:0) are two saturated fatty acids of the kernel oil, while oleic acid (C18:1) and linoleic acid (C18:2) are the unsaturated fatty acids which constitute 53.25 and 25.95% of the total fatty acids. The chemical composition of the seeds makes them a good source of edible oil with high nutritional value (Embaby and Mokhtar 2011).

2.4 In Vitro and In Vivo Pharmacological Uses

The dependence on nature to treat human diseases and disorders was established by observation as well as by trial and error method. Edible medicinal plants such as *ZSC* have an imperative role in retentive human health and longevity. *Ziziphus* species with enormous folklore claim are considered as a persuasive resource of therapeutic agents due the presence of a diverse range of pharmacologically active biomolecules. Scientific evidence reported on this plant divulge its valuable application in the field of pharmacy. The exploration of therapeutic potential of *ZSC* has revealed it to possess antimicrobial, anticancer, antidiabetic, antinociceptive, antihypertensive, antidiarrheal, and CNS effects (Fig. 2.8). It has been recommended that further investigations of their bioactive composition are essential to fully recognize the molecular mechanisms of their in vitro and in vivo therapeutic effect and to declare that the extracts are safe for human use. In this chapter, the experimental evidence of animal and human studies reported so far for the *ZSC* are described with the cynosure that the plant has been traditionally used to treat various diseases as mentioned in Table 2.3. In vitro and in vivo pharmacological activities of the *ZSC* studied for the treatment of different ailments and disorders are summarized as follows:

2.4.1 Antimicrobial Activity of *ZSC*

ZSC has been reported to contain a number of secondary plant metabolites that are primarily responsible for their broad spectrum of biological activity. *ZSC* has been shown to exhibit antimicrobial activity against bacteria, virus, and fungi in addition to its activity against other drug-resistant pathogenic species (Fig. 2.9) (Nazif 2002). Antibacterial effects of *ZSC* could be attributed to the presence of tannins (Elboosaty 2020). This is due to the fact that the tannins are associated with the protein, especially proline-rich proteins, and they bound to the iron, which contributes to the inhibition of the metabolism inside the microbe and helps to eliminate it (Michel et al. 2011). Saponin content of *ZSC* also plays a major role in manipulating the surface tension of the cell membranes, which leads to increasing the permeability of cells and hence could produce bactericidal effect (Arabski et al. 2012; Huang et al.

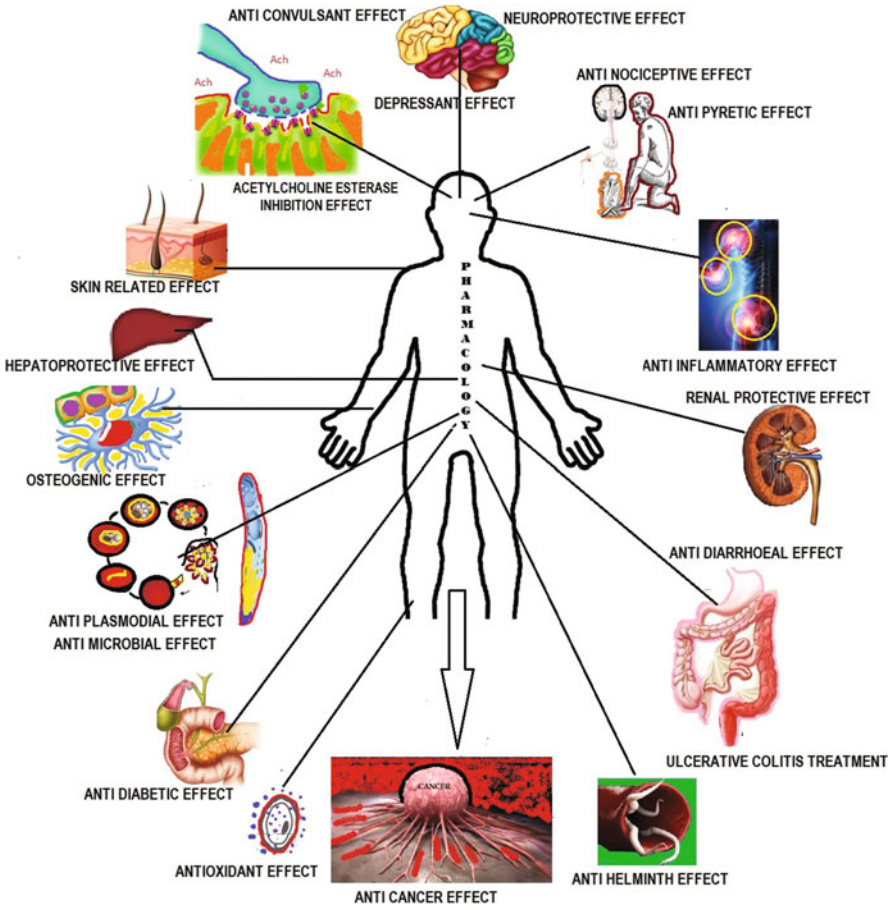


Fig. 2.8 In vitro and in vivo pharmacological effects of *Ziziphus spina-christi*

2018). The cyclopeptide alkaloids have the ability to inhibit the cell division/multiplication in microbes by binding to microbial DNA. Flavonoids could also be responsible for the antimicrobial activity as these can bind to DNA and RNA, thereby inhibiting protein and fat formation, causing energy metabolism to be impaired, thereby affecting the growth of the microbe (Panche et al. 2016). The details of the reported scientific evidences on the antibacterial, antifungal, and antiviral properties of various parts of *ZSC* are given in Table 2.3.

Table 2.3 Evaluation reports of antibacterial, antifungal, and antiviral activity of various parts of *ZSC*

Plant parts	Extract	Method	Organism tested	Standard	Notable results	Evidence reported
Antibacterial activity reports						
Stem bark	Ethanol, ethyl acetate, alkaline ethyl acetate	Agar well diffusion	*S. pneumoniae*, *B. subtilis*, *P. aeroginosa*, *E. coli*	Amphotericin B, ampicillin, gentamicin	Ethyl acetate extract is more effective	Ads et al. (2017)
Fresh fruit/ Fruit oil	n-hexane	Disc diffusion	Phytopathogenic bacteria: *P. carotovorum*, *D. solani*, *R. solanacearum*, *E. cloacae*, *B. pumilus*	Gentamicin 20 µg/disk	Different levels of activities	El-Hefny et al. (2018)
Leaf, Fruit	Aqueous, methanol	Agar well diffusion	*B. subtilis*, *B. aquimaris*, *C. michiganensis*, *E. coli*, *E. amylovora*, *P. syringae*	Ampicillin 50 mg/mL	Activity only against gram-positive bacteria	Mohamed et al. (2017)
Leaf, Stem bark, Leaf+ stem bark	Aqueous	Well diffusion	*K. pneumoniae*, *S. saprophyticus*, *S. pneumonia*, *Acinetobacter* spp., *E. coli*, *Serratia* spp., *S. typhi*, *P. aeroginosa*, *S. epiderdimis*, *S. pyogenes*, *S. aureus*, *Proteus mirabilis*, *Enterobacter* spp.	None reported	Organisms highly sensitive to combination of leaves and stem bark extract	Jebur et al. (2020)
Leaf	Aqueous, ethanol	Agar well diffusion	Hospital sample isolates: *B subtilis*, *E. coli*	None reported	Ethanol extract is more effective	Ebid (2015)
Fruit, leaf, seed, stem	Petroleum ether, chloroform, methanol, aqueous	Cup plate agar diffusion	*B. subtilis*, *S. aureus*, *E. coli*, *K. pneumoniae*,	Ampicillin, gentamicin, tetracyclin, 5–40 µg/mL	Methanol extracts of all parts are effective against the tested organism and	Ali et al. (2015)

			P. vulgaris, *P. aeruginosa*		aqueous extract was inactive	
Leaf, fruit, seed	Petroleum ether, chloroform, ethanol, water extracts and fractions	Microtitre plate dilution	*B. cereus*, *S. aureus*, *S. pyogenes*, *E. coli*, *E. cloacae*, *K. pneumoniae*, *P. vulgaris*, *P. aeruginosa*, *S. typhimurium*, *acid-fast bacilli M. fortuitum*	None reported	Chloroform extract of leaf and seed showed inhibitory and bactericidal activity against gram-positive microorganisms	Shahat et al. (2001)
Fruit-seed	Lipid content of seeds—its saponifiable and unsaponifiable fraction	Diffusion assay method	*B. subtilis*, *S. pyogenes*, *E. coli*, *S. cereviciae*	Ampicillin	Fatty acid fraction of lipids of seeds was active against *B. subtilis*, *E. coli*, *S. pyogenes*	Nazif (2002)
Leaf, Bark	Methanol	Cup plate agar diffusion	*E. coli*, *S. aureus*, *K. pneumonia*	None reported	Effective against *S. aureus* and *K. pneumoniae*	Mohamed et al. (2010)
Fruit-seed oil	Oil extract	Agar well diffusion	*Shigella* spp., *S. aureus*, *P. aeruginosa*, *E. coli*	Chloramphenicol 30 mg	Seed oil is active against *S. aureus* and *E. coli*	Bukar et al. (2015)
Bark, fruit, root, seed, leaf	Methanol, ethanol	Agar well diffusion	*P. aeruginosa*, *E. aerogenes*, *E. coli*, *K. pneumoniae*, *E. cloacae*, *E. faecalis*, *MRSA*	Erythromycin 50 mg/mL	*E. coli* and *MRSA* were moderately sensitive to extracts and resistant to erythromycin	Temerk et al. (2017)
Leaf	Aqueous, ethanol	Disk diffusion	*E. coli*, *S. aureus*, *K. pneumoniae*	Chloramphenicol 250 mg/mL	Highly effective against *E. coli*	Alhassan et al. (2019)
Stem bark	Petroleum ether, ethyl acetate, ethanol, methanol aqueous	Cup plate agar diffusion	*E. coli*, *P. aeruginosa*, *B. subtilis*, *S. aureus*	None reported	Methanol extract showed high activity at all concentrations	Makhawi et al. (2020)

(continued)

Table 2.3 (continued)

Plant parts	Extract	Method	Organism tested	Standard	Notable results	Evidence reported
Fruit	Ethanol, ethyl acetate	Modified agar diffusion	*S. aureus*, *E. coli*, *P. aeruginosa*, *S. aureus*, *E. faecalis*, *E. coli*, *E. faecalis*, *P. aeruginosa*	Ampicillin, gentamycin 10 μg/disk	Ethyl acetate extract was most active	Ali et al. (2001)
Leaf, seed	Aqueous, methanolic	Agar well diffusion	*Isolated from skin lesions: S. aureus*, *P. aeruginosa*, *E. coli*, *Acinetobacter* spp., *Enterococcus* spp.	Tetracyclin 30 mg	Aqueous leaves extract was effective against *S. aureus*	Al-Bayatti et al. (2011)
Leaf, fruit	Aqueous extracts	Agar diffusion	*S. aureus isolated from burn cases*	Penillin G, kanamycin, cephalexin, tetracyclin, neomycin, genetamicin, fusidic acid, tobramycin	Effective bacteriostatic action on *S. aureus* (750 and 1000 mg/mL)	Alsaimary (2009)
Leaf, flower, stem, young branch, fruit, root	Ethanol, aqueous	Disk diffusion	*S. aureus*, *K. pneumoniae*, *P. vulgaris*, *P. aeruginosa*, *E. coli*	Ampicillin, penicillin G, gentamicin	Ethanol extract has moderate effect on gram-negative bacilli	Ali-Shtayeh et al. (1998)
Leaf	Ethanol	Disk diffusion	Isolated from infected patient's urine, stool, blood and wounds: *S. aureus*, *Methicillin- and cefixime-resistant S. aureus strains*	None reported	Effective towards *MRSA* strains	Moghadam et al. (2010)
Leaf	Ethanol, methanol	Disk diffusion	*S. typhi*, *P. mirabilis*, *S. dysenteriae*, *E. coli*, *K. pneumoniae*,	Novobiocin Naficillin Colistin	Ethyl acetate extract was most active	Motamedi et al. (2014)

			B. melitensis, *B. bronshiseptica*, *P. aeruginosa*			
Stem bark Leaf	Ethanol, petroleum ether, ethyl acetate, aqueous, methanol	Agar well diffusion	*S. aureus*, *B. subtilis*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, *S. paratyphi B*, *K. pneumoniae*	Gentamicin, tetracycline, ampicillin 40 mg/mL to 5 mg/mL	Ethanol extract was effective against all tested bacteria except *E. coli*	El-Kamali and Mahjoub (2009)
Leaf	Ethanol, methanol	Disk diffusion	*S. aureus*, *E. coli*, *K. pneumoniae*, *Salmonella* sp., *P. mirabilis*, *P. aeruginosa*, *Enterobacter* sp.	Amikacin, vancomycin, clarimazole, doxycycline, ceftazidime, neomycin, novobiocin	Extracts showed a stronger effect than standard antibiotic disks	Al-Mutairi et al. (2016)
Fruit	Methanol	Agar well diffusion	*S. aureus*, *S. epidermidis*, *E. faecalis*, *B. cereus*, *K. pneumonia*, *E. coli*	Chloramphenicol 5 mg/mL)	Moderate activity against the gram-positive bacteria	Abdallah (2017)
Pulp	Aqueous	Agar plate diffusion	*S. aureus*, *P. aeruginosa*, *S. pyogenes*, *E. coli* laboratory isolates	None reported	Effective against *E. coli* and *P. aeruginosa*	Tom et al. (2009)
Stem bark	Ethanol, chloroform, petroleum ether, ethyl acetate, butanol	Disk diffusion	*E. coli*, *P. aeruginosa*, *Bacillus* spp., *S. aureus*	None reported	Ethanol extract of bark showed bactericidal and bacteriostatic activity against all organisms	Alomari et al. (2017)
Leaf	Methanol, water	Agar diffusion	*B. subtilis*, *B. aquimaris*, *C. michiganensis*, *E. coli*, *E. amylovora*, *P. syringae*	Kanamycin for *B. subtilis* and *B. aquimaris*; ampicillin for *E. coli* and *E. amylovora*	Methanol extract was more effective against gram-negative bacteria when compared to the aqueous extract	Mohamed et al. (2017)

(continued)

Table 2.3 (continued)

Plant parts	Extract	Method	Organism tested	Standard	Notable results	Evidence reported
Leaf, bark	Dichloromethane, ethyl acetate, ethanol	Micro-dilution	*B. subtilis*, *S. aureus*, *E. coli*, *K. pneumoniae*	Neomycin	Weak antibacterial activity	Eldeen and Van Staden (2007)
Honey	Fresh samples	Well diffusion	*B. cereus*, *S. aureus*, *E. coli*, *S. enteritidis*	Tetracycline chloramphenicol	Effective bactericidal	Owayss et al. (2020)
Antifungal activity reports						
Unripe and ripe fruit	Ethanol	CLSI M27-A3 standard method	Isolated from the oral cavity of the liver transplant patients*:* *C. albicans*, *C. glabrata*	Nystatin, fluconazole	Unripe fruits was more effective than fluconazole	Mardani et al. (2018)
Leaf	Aqueous	Agar dilution	*Fusarium* sp., *Alternaria* spp., *Trichoderma* sp., *Colletotrichum* sp., *Drechslera* sp., *Fusariumoxysporum*, *Helminthosporium* sp., *Rhizoctonia solani*, *Macrophomina phaseolina*, *R. solani*	None reported	Significant activity against the growth of overall tested fungal genera	Alotibi et al. (2020)
Fruits, leaf, seed, stem	Petroleum ether, chloroform, methanol, aqueous	Cup plate agar diffusion	*A. niger*, *C. albicans*	Clotrimazole, nystatin	Not effective	Ali et al. (2015)
Leaf, flower, stem, young branch, fruit, root	Ethanol, aqueous	Disk diffusion	*C. albicans*	Nystatin	Not effective	Ali-Shtayeh et al. (1998)

Fruits	Aqueous extract	Agar disk diffusion method	*C. albicans*	Amphotericin B (5 mg/mL)	Extract showed promising anti-Candida activity	Pibalouti et al. (2009)
Leaf, fruit, seed	Petroleum ether, chloroform, ethanol, water	Microtitre agar plate	*C. albicans*, *A. niger*, *T. rubrum*	None reported	Chloroform leaves extract was moderately effective against the *T. rubrum*	Shahat et al. (2001)
Stem bark	Ethanol Ethyl acetate	Agar well diffusion assay	*A. fumigatus*, *S. racemosum*, *G. candidum*, *C. albicans*	Amphotericin B	AEA extract was effective against *A. fumigatus*, *S. racemosum*	Ads et al. (2017)
Pulp	Aqueous	Agar plate diffusion	*C. albicans*	None reported	Extract was effective	Tom et al. (2009)
Stem bark	Ethanol, petroleum ether, chloroform, ethyl acetate, butanol	Disk diffusion	*C. albicans*	None reported	Ethanol extract of bark was mildly effective	Alomari et al. (2017)
Fruit-seed	Lipid content of seeds—its saponifiable and unsaponifiable fraction	Diffusion assay method	*A. niger*, *A. flavus*	Canesten	Slight activity	Nazif (2002)
Antiviral activity reports						
Leaf, fruit, seed	Petroleum ether, chloroform, ethanol, aqueous	Host cell monolayer (Vero cells) infected with tested virus is used	*Herpes simplex type 1 (HSV1), measles Edmondston A (MEA), poliomyelitis virus type 1 (polio 1), vesicular stomatitis virus (VSV)*	None reported	Ethanol fraction of the fruits and the aqueous extract of the leaves were effective against *HSV1*	Shahat et al. (2001)
Leaf, bark	Methanol	Cup plate agar diffusion	*New castle disease, fowlpox viruses*	None reported	Extract showed mild antiviral activity	Mohamed et al. (2010)

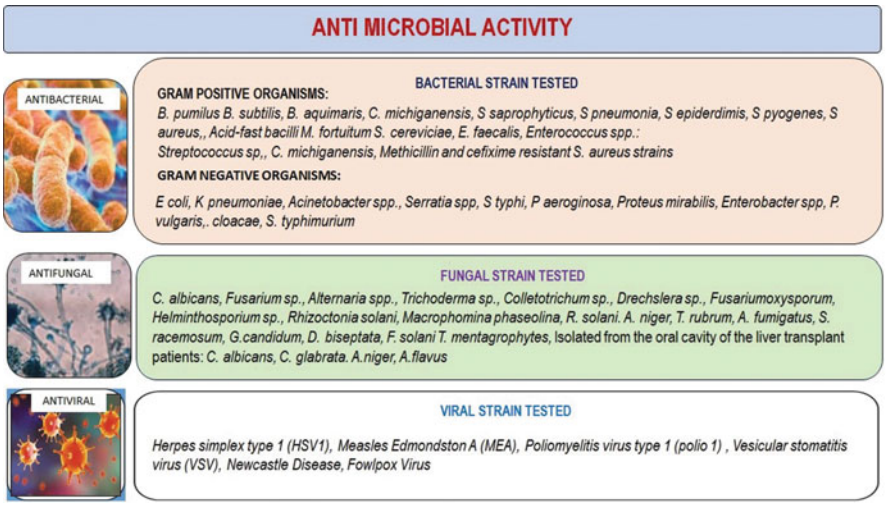


Fig. 2.9 Microbial strains used for the study of antimicrobial effects of *ZSC*

2.4.2 Antioxidant Activity of *ZSC*

In vitro antioxidant activity of *ZSC* fruits, leaf, bark, and seeds has been assessed using a variety of assay methods (Fig. 2.10), and the results indicate that *ZSC* exhibits robust free radical scavenging activity.

ZSC fruits (429 μg/mL) grown in Oman showed 91% inhibition in the ABTS method, 51% inhibition (at 140 mg/mL) of DPPH radical scavenging, and 47% of inhibition in the SRSA assay (at 20 μg/mL). The *ZSC*F extract could chelate ferrozine and form complexes with ferrous ions (Singh et al. 2012). The ethanolic extract of the dry seeds and fruit powder of *ZSC* grown in Oman showed DPPH scavenging activity in a dose-dependent manner, in which fruit extract exhibited (54.1%) inhibition at 200 μg/mL whereas seed extract showed only 42.6% inhibition at the same concentration. Contrary, *ZSC* seeds were found to contain the highest total phenolic content (Al Hakmani et al. 2014). Methanolic leaves extracts of five *ZSC* provenances (INRGREF, Tozeur, Degueche, Nafta, and Kebelli) showed that the Kebelli provenance *ZSC* has high antioxidant activity (0.086 μg/mL) in a DPPH assay (Elaloui et al. 2017). Methanolic extracts of *ZSC* leaves proved to have the highest phenolic content along with antioxidant activities (93.6%) with respect to standard ascorbic acid (87.4%) (Tawfik et al. 2015). Various concentrations of methanolic, aqueous, and ethanolic extracts of the *ZSC* leaves in the DPPH and reducing power assay methods revealed to possess concentration-dependent antioxidant activity with IC_{50} values of 21.4 and 24.2 μg/mL (Khaleel et al. 2016). Radical scavenging activity of ethanolic leaves extract is better than the hexane extracts (Abalaka et al. 2011). The ethyl acetate fraction of leaves extract exhibited higher inhibition of DPPH radical (96%) in comparison to the standard butylated hydroxyl anisole, n-butanol, and aqueous extracts. The total antioxidant activities of methanol,

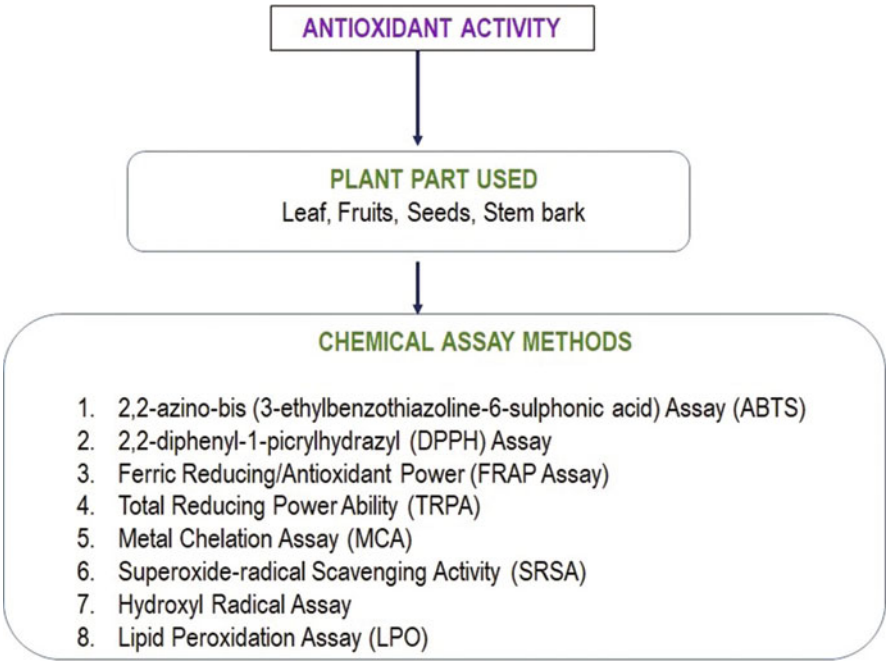


Fig. 2.10 Chemical assay methods and plant parts used for the determination of antioxidant activity of *ZSC*

ethanol, ethyl acetate, and aqueous extract range from 70.5 to 91.2% inhibition in the ABTS assay method (Al-Ghamdi and Shahat 2017). The total alcoholic extract of the plant leaves and stem bark has shown significant antioxidant effect (Adzu et al. 2003; Mohamed et al. 2017). Crude juices of Sidr (*ZSC*) leaves reported to exert effective antioxidant capacity by DPPH free radical scavenging method. It was reported that the administration of Sidr juice (leaves) did not cause any changes in liver and kidney functions proving their antioxidant ability in vivo (Al-Marzooq 2014). *n*-Butanol extracts of leaves of Omani *ZSC* have also been shown to exhibit antioxidant activity and radical scavenging activity (Al-Busafi et al. 2007). In general, the variation in the activity and chemical constituents like mineral level, polyphenolic content, and antioxidant capacity could be due to the difference in *Ziziphus* species, part of the plant analyzed, and its vegetation region (El-Maaiden et al. 2020).

2.4.3 Antipyretic Effect of *ZSC*

Traditional claim postulates that *ZSC* have antipyretic effect (Table 2.1), but the literature survey revealed only one study for evaluation of antipyretic activity has been carried out so far and the reason behind this is unknown. Tanira et al. (1988)

reported that the ethanolic extract of *ZSC* leaves exhibited a significant, though a moderate, antipyretic effect on hyperpyrexia-induced mice and are supporting the traditional claim (Tanira et al. 1988).

2.4.4 Antidiuretic Activity of *ZSC*

Diuretic activity of ethanolic extract of *ZSC* leaves in rats (500 mg/kg) was reported. Sodium and potassium content of the urine was determined using flame photometry to investigate the effect, but the extract failed to demonstrate any promising effect (Tanira et al. 1988). No other studies were undertaken to determine the antidiuretic activity of the *ZSC* plant extracts.

2.4.5 Anticancer Activity of *ZSC*

Therapeutic application of plant products in the management of cancer has gained a prominent role in medical field. The anticancer properties of *Ziziphus* plant has been believed by the people from different regions especially from China, Iran, and Arabia (Bown 1995; Vahedi et al. 2008; Deshpande et al. 2019). The honey of *ZSC* is considered as an alternative cytotoxic agent and was administered to patients suffering from different types of cancers including colon, breast, and liver cancers (El-Gendy 2010). The leaves extracts of *ZSC* have prominent cytotoxic activity against cancers of the cervix and the breast, and the aqueous fruit extract is effective against breast cancer (Jafarian et al. 2014; Farmani et al. 2016). Cytotoxic activity of *ZSC* leaves extract was explored scientifically, but it was not compared with any other plant parts of *ZSC*; however, variable cytotoxic activities may be attributed to different parts of the plant like fruits, seeds, and stem (Soliman et al. 2019). Pharmacological activity index and phytoconstituents of the same plant vary depending on the environmental climates and in turn may lead to genetic and chemical variations among individuals of the same species (Moustafa et al. 2016).

Fractions of different parts of the *ZSC* grown in the unique environmental conditions of UAE were tested against several cancer cell lines. The results indicated that the ethanolic extract of stem exhibited superior anticancer activity than that of the leaves and thorns. The stem extract showed potent and specific effect on HEPG2 cancer cells with a survival rate of 5% compared to 8%, 19.5%, and 21% survival rates for A549, MDA, and U87cells, respectively, and traditional claim of *Ziziphus* spp. as an alternative anticancer agent could be attributed to the presence of betulin derivatives (Soliman et al. 2019). The ethanolic fraction of leaves extract had the lowest IC_{50} value (0.02 mg/mL) and induced cell cycle arrest at the G1/S phase as well as apoptosis against MCF-7 (human breast adenocarcinoma) cell lines. The most active fraction of *ZSC* against breast cancer cell line was identified by fractionation strategy, and the results demonstrated that apoptosis induction mechanism is through a mitochondrial-independent pathway. Among all the fractions tested for cytotoxic effects in MCF-7 cells, ethanolic fraction was found to be highly active

with an IC_{50} of 0.02 mg/mL after 48 h of incubation at ½ IC_{50} concentration (Farmani et al. 2016). It has been established previously that induction of apoptosis is one of the mechanisms for the anticancer activities of *ZSC* extracts in different cancer cell lines (Huang et al. 2007). *ZSC* leaves extracts exhibit its cytotoxic effect through Bax-independent apoptotic pathway on MCF-7 cells (Ghaffari et al. 2020). The methanolic extract of the leaves of *ZSC* exhibited anticancer effect against diethylnitrosamine (DENA)-persuaded hepatocarcinoma in rats and is quantified through the expression of hepatocyte growth factor, insulin-like growth factor-1 receptor, B cell lymphoma-2, and matrix metalloproteinase-9 oncogenes (El-Din et al. 2019). It has also been reported that the dried *Ziziphus* plant has anticancer activity (Bown 1995; Vahedi et al. 2008). *ZSC* exhibits proapoptotic mechanism and is evident by the increased levels of cleaved caspase-3. An in vivo study concluded that *ZSC* extract could inhibit the early stage of colon carcinogenesis by preventing oxidative stress and inducing apoptosis (Guizani et al. 2013). The protective effects of *ZSC* fruit extract against 1-methyl-4-phenylpyridinium (MPP^+)-induced neurotoxicity in SH-SY5Y cell lines depict that protective effect of ZSC fruits might be mediated by its potent antioxidant properties (Singh et al. 2018). While discussing the reported anticancer activity, it has been observed that only tumor cell lines were used to evaluate the cytotoxic effects of *ZSC* extracts and the in vivo preclinical evaluations are very minimal. No clinical trials have been conducted in humans to examine the pharmacokinetics and therapeutic action of these compounds and extracts on cancer patients. Future research should emphasize on in vivo preclinical studies and clinical trials (Ghaffari et al. 2020).

2.4.6 Acetylcholinesterase Inhibitory Effect of *ZSC*

ZSC bark, leaves, and root showed inhibition effect on acetylcholinesterase enzyme by Ellman's method, and it sturdily supports further investigation into pharmacotherapeutics (Eldeen and Van Staden 2007). As per the traditional claim (Table 2.1), it has been apparent that *ZSC* possess pharmacological action related to nervous system, but till date the scientific evaluation regarding the cholinesterase inhibition effect is scarce. Dichloromethane, ethyl acetate, and ethanol extracts of *ZSC* plant parts were investigated for acetylcholinesterase inhibition effect. Moderate inhibitory activity is exhibited by dichloromethane and ethyl acetate (leaf and bark) extracts of *ZSC* (range of IC_{50} value was 1.0–0.3 mg/mL). The lowest IC_{50} value was detected with ethanolic extracts of the bark and root of *ZSC* (0.09 mg/mL) (Eldeen and Van Staden 2007).

2.4.7 Antidiabetic Activity of *ZSC*

ZSC is reported traditionally as a versatile hypoglycemic agent. Researches indicated that aqueous extract of plant decreases the level of blood glucose by two mechanisms by acting on glucose homeostasis in an extra-pancreatic way or by

improvement of liver action in diabetic rats. Saponin glycosides present in this plant are responsible for lowering level of glucagon (Elboosaty 2020; Deshpande et al. 2019). The hypoglycemic and antidiabetic activities of methanol extract (*ZSC*-1) as well as ethyl acetate (*ZSC*-2), n-butanol (*ZSC*-3), and aqueous (*ZSC*-4) fractions of *ZSC* leaves were evaluated in diabetic mice and compared with glibenclamide, and it was observed that fraction *ZSC*-3 displayed potential hypoglycemic activity (Al-Ghamdi and Shahat 2017). Effects of butanol extract of *ZSC* leaves and its principle saponin glycoside christinin A were evaluated in normal and streptozotocin diabetic rats. It has been reported that after 4 weeks of treatment, both the agents significantly reduced the level of serum glucose and activity of liver phosphorylase and glucose-6-phosphatase (G-6-Pase). Serum insulin and pancreatic cAMP levels also showed a significant increase with the butanol extract-treated diabetic rats (Glombitza et al. 1994). Avizeh et al. (2010) reported that the hydroalcoholic extract (500 mg/kg) of *ZSC* fruit had a mild, but significant, blood glucose-lowering effect after 10 days of oral administration to diabetic rats, and it also showed a simultaneous increase in the serum insulin level. Hence the long-term use of this agent may be advantageous over conventional drugs in relieving some of the complications caused by diabetes (Avizeh et al. 2010). Polysaccharides from *Ziziphus* spp. significantly lowered the levels of LDL cholesterol, triglycerides, total cholesterol, and very-low-density lipoprotein (VLDL) cholesterol and evidently increase the high-density lipoprotein (HDL) cholesterol levels in a fructose-induced animal model of diabetes (Zheng et al. 2019; Pandey et al. 2011). The antidiabetic effects of fruit extracts of *ZSC* in alloxan-induced diabetic rats showed a dose-dependent positive effect (Abubakar et al. 2018). In vitro α-glucosidase and α-amylase inhibitory activities for different concentrations of methanolic and ethanolic leaves extracts of *ZSC* were reported. Methanolic extract seems to be very potent in inhibiting both enzymes compared to ethanolic extract. The calculated IC_{50} was 8.9 and 305.6 μg/mL against α-glucosidase and 39.12 and 318.4 μg/mL against α-amylase for methanolic and ethanolic leaves extracts, respectively (Khaleel 2018b). Leaves of Christ's thorn are reported to possess antihyperglycemic activity, and triterpenoidal saponin glycosides, christinin A, B, C, and D, isolated from the butanol extract play a major role in the therapeutic activity of the plant (Mahran et al. 1996).

Butanol extract of *ZSC* leaves decreased the serum glucose level in control as well as in type-II diabetic rats. This antidiabetic response was arbitrated by releasing insulin, and this insulin tropic effect of *ZSC* leaves might be due to blockade of K-ATP channels of the pancreatic beta-cell membranes (Abdel-Zaher et al. 2005). Administration of 100 mg/kg *ZSC* leaves extract greatly ameliorated the diabetic disorders in rats (Parsaeyan and Rezwani 2014). Administration of *ZSC* ethanolic leaves extract (200 mg/kg b.w.) and plain and formulated soft gelatin capsules (450 mg) for 28 days in STZ diabetic rats revealed better glucose utilization by increasing insulin secretion and C-peptide levels with stabilization of percentage of glycated hemoglobin (HbA1C%) (Michel et al. 2011). It has been reported that pretreatment either with 100 mg/kg butanol extract or christinin A improved glucose-induced insulin release in non-diabetic control rats. Pretreatment with the

butanol extract or christinin A improved the oral glucose tolerance in type-II model; however there was no response in type-I diabetic rats (Abdel-Zaher et al. 2005).

2.4.8 Antidiarrheal Activity of *ZSC*

The fruits of *ZSC* administered in an adequate amount act as a laxative and decrease water maintenance, and the leaves have the ability to kill diarrhea-causing parasites and worms in the intestinal tract (Saied et al. 2008; Jongbloed 2003). In Sudan, *ZSC* root infusion is administered for the treatment of dysentery (El Ghazali et al. 1997). A preclinical study reported that methanol extract of *ZSC* of the stem bark possess antidiarrheal effect (Adzu et al. 2003). The accumulation of intraluminal fluid and gastrointestinal transit time were measured, and it was shown that the extract caused a dose-dependent protection of rats against castor oil-induced diarrhea and showed a prominent decrease in the intraluminal fluid accumulation and gastrointestinal transit time. Biologically active components like glycosides, resins, saponins, and tannins in *ZSC* extract may be useful against diarrhea, thereby vindicating its use in traditional practice as an antidiarrheal agent (Adzu et al. 2003, 2007a, b).

2.4.9 Anti-Inflammatory Activity of *ZSC*

ZSC is commonly used in traditional medicine across the gulf region for the management of pain and inflammatory-related problems (Asgarpanah and Haghighat 2012; Waggas and Al-Hasani 2009). The anti-inflammatory effects of fruits, seeds, and leaves of *ZSC* extracts were reported. The alcoholic extract of *ZSC* leaves reported a highly significant anti-inflammatory activity ($p < 0.05$), and the maximum effect (38%) was at 3 h, whereas the standard oxyphenbutazone showed much more significant reduction (65%) (Tanira et al. 1988). Anti-inflammatory activity of *ZSC* fruit/seed extracts was evaluated by an in vitro pilot study. The seed extract showed a significant difference in the inhibition of thermally induced protein denaturation when compared with fruit extract at concentrations of 100 and 500 μg/mL (Al Hakmani et al. 2014). Anti-inflammatory activity of methanolic extract against acetic acid (AcOH)-induced colitis in rats was reported. Administration of extract (400 mg/kg) resulted in a better reduction of inflammatory colonic injury than standard drug mesalazine (MLZ). Moreover, it effectively moderated the mRNA expression of redox-sensitive transcription factors like nuclear factor (erythroid-derived 2) and heme oxygenase-1 and also downregulated the expression of p38 mitogen-activated protein kinase and upregulated the vascular endothelial growth factor A and interleukin-1β in AcOH-induced colitis in rats. Hence, it could be considered as an alternative therapeutic option for the management of inflammatory bowel diseases (Almeer et al. 2018). Methanolic extract of *ZSC* leaves seems to be a strong potent in both enzymes inhibitory potential compared to ethanolic extract. At the concentration of 100 μg/mL, the anti-inflammatory effects were

95.3, 25.2, and 20.2% for methanolic extract, ethanolic extract, and standard diclofenac sodium, respectively (Khaleel 2018b).

New anti-inflammatory compounds from *ZSC* have been identified from ancient Egyptian prescriptions such as epigallocatechin, gallocatechin, spinosin, 6″' feruloylspinosin, and 6′" sinapoylspinosin which are crucial for pharmacological activity of crude extracts of seed, leaf, root, or stem playing a major role in the inhibition of NF-κB pathway (Kadioglu et al. 2016). *Ziziphus* species extract sharply increased the homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) and reduced the atherogenic index (AI) in mice exposed to high fructose water (Zheng et al. 2019). Sepsis induced by cecal ligation and puncture in mice was treated with *ZSC* leaves extract, and it exerted a myocardial and renal protective effect. Prophylactic treatment with *ZSC* leaves extract (100, 200, and 300 mg/kg) maintains the normal heart rate (HR); decreased the elevated levels of malondialdehyde; the activity of myeloperoxidase, nitric oxide (NO), and inducible NO synthase; and the expression of nuclear factor kappa B (NF-κB); but increased the content of glutathione and antioxidant enzyme activities in mice with sepsis. Lower levels of cytokines, including TNF-α and interleukin (IL)-1β, were evident from biochemical analyses, and qRT-PCR indicated that *ZSC* leaves extract treatment reduced myocardial and renal apoptosis. This effect may be attributed to the antioxidant, anti-inflammatory, and antiapoptotic activities of *ZSC* leaves extract (Dkhil et al. 2018a, b).

2.4.10 CNS-Related Activity of *ZSC*

ZSC possess anticonvulsant, neuroprotection, and CNS depression activity. The genus *Ziziphus* is proved to be effective on CNS (Kaleem et al. 2014). Anticonvulsant activity of *ZSC* extract is through the inhibition of the neurotransmitters at different brain regions. Intraperitoneal injection of *ZSC* leaves extract (50 mg/kg body weight) for 15 days and consequent withdrawal of extract administration produced a significant increase in the release of neurotransmitter in different parts of the brain of male albino rats. The inhibition of calcium-ATPase and phosphodiesterase leads to the increase in neurotransmitter content in CNS areas, and also at the same time, it inhibits Ca^{2+} calmodulin binding. It has been correlated that the ability of this plant extract to depress excitable tissue at all levels of the CNS directs to a decrease in the amount of transmitter released by the nerve impulse, as well as it leads to general depression of postsynaptic responsiveness and ion movement (Waggas 2006). The aqueous extract of roots of *ZSC* has pharmacological effect on exploratory behavior, spontaneous motor activity (SMA), pentobarbital-induced hypnosis, and motor coordination. It was found that this extract has a CNS depression activity (Adzu et al. 2002). *ZSC* leaves extract was examined for its anticonvulsant effect by using pentylenetetrazol (PTZ) model on male albino rats. It was concluded that the presence of peptide and cyclopeptide alkaloids in the *ZSC* leaves extract caused a decrease in NE, DA, and 5-HT contents in PTZ model (Waggas and Al-Hasani 2010). *ZSC* improved motor coordination in rats and shortened step-

through latency in Morris water maze test. Hydroalcoholic extract of *ZSC* leaves significantly ameliorated scopolamine-induced anxiety in rats (Setorki 2016).

ZSC ethanolic leaves extract showed neuroprotective activity against brain ischemia (induced), so it has the ability to decrease the brain damage caused by transient global cerebral ischemia and reperfusion (Setorki and Hooshmandi 2017). The protective effect on the cerebral oxidative stress and impairment induced by ischemia was mainly due to the increased activity of antioxidant defense system and inhibition of oxidative stress in the rat's brain. Other studies also reported the antioxidant activity of *ZSC* extract and its relation with neuroprotection (Abalaka et al. 2011; Michel et al. 2011). The phytoceutical from hexane extract of *ZSC* root bark (25, 50, and 100 mg/kg, p.o.) was tested against pentobarbital sleeping time, motor coordination test, and exploratory behavior in mice. Results showed that extract prolonged pentobarbital-induced hypnosis and decreased the head-dip responses in the exploratory behavior. However, it failed to give a positive result on the motor coordination test. These results demonstrated the potent central depressant effect of *ZSC* extract (Adzu et al. 2008). The pharmacological activity of *ZSC*F extract against 1-methyl-4-phenylpyridinium (MPP^+)-induced neurotoxicity in SH-SY5Y (neuronal) cell lines was evaluated. The effect of ZSCF on MPP^+-induced cell viability, membrane damage, and oxidative stress; mitochondrial membrane potential and activity of caspase-3, and protein expressions and apoptotic effect of cyto C, Bax, and Bcl-2 were measured. The results showed that *ZSC*F could be able to reduce the neurotoxicity of MPP^+ and offer neuroprotection in vitro and is reinforced by its potent antioxidant properties (Singh et al. 2012).

2.4.11 Antinociceptive Activity of *ZSC*

ZSC extract has the ability to suppress central and peripheral phases of nociception. The aqueous extract of *ZSC* root bark relieves pain via central and peripheral mechanisms and hence provides some justification for the folkloric use in the treatment of stomach pains (Adzu et al. 2001). Central analgesic activity of the extract is confirmed by the increase in the mean percentage effect on the hot plate test. *ZSC* aqueous extract of the leaves established a dose-dependent analgesic effect at different concentrations (250–1000 mg/kg), and it helps to reduce the number of writhes induced by a 0.6% aqueous solution of Ac-OH in Wistar rats. It has been reported that the aqueous extract of *ZSC* leaves (250 mg/kg) produced a similar effect to that of pethidine hydrochloride (10 mg/kg) (Effraim et al. 1998). Aqueous extracts of *ZSC* revealed a dose-dependent analgesic effect. With the aim of elucidating both central and peripherally mediated action in rats and mice, the chloroform and methanol fractions (70:30) of *ZSC* root (25, 50, and 100 mg/kg, i.p.) were tested on chemical (Ac-OH-induced writhing, formalin), mechanical (analgesiometer), and thermal (tail-flick) analgesic tests (Adzu and Haruna 2007). Contrary, alcoholic extract of *ZSC* leaves (500 mg/kg) failed to produce antinociceptive effect in tested rats (Tanira et al. 1988).

2.4.12 Anthelmintic Activity of *ZSC*

Antieimeria and anthelmintic activity of *ZSC* leaves extract at a dose of 100, 200, and 300 mg/kg was evaluated. For antieimeria activity, the mice infested with 1.2 × 103 *E. papillata*-sporulated oocysts were used. The anthelmintic potential of *ZSC* extract was investigated on adult earthworm, *Allolobophora caliginosa*. *ZSC* leaves extract significantly reduced the shedding of oocysts to about 10.7×10^3, 28.3×10^3, and 23.8×10^3 oocysts/g feces in 100, 200, and 300 mg/kg groups and was able to improve the induced jejunal injury by *E. papillata* infection by paralysis and death of worms (Alzahrani et al. 2016). The fact that *ZSC* holds anticoccidial activity has also been detailed in mice infected with *Cryptosporidium* spp. (Kadir et al. 2008). The mechanism of anticoccidial properties caused by *ZSC* was also similar to those occurring with most anticoccidial drugs (Wunderlich et al. 2014). Also, *ZSC* leaves extract has the ability to improve the histological damage done by *E. papillata*. In vitro and in vivo anthelmintic efficacy of aqueous and methanolic extracts of *ZSC* was proved using live *Haemonchus contortus* and experimentally induced *Haemonchus contortus* infection in Nubian goats. Crude aqueous extract and crude methanolic extract of *ZSC* leaves showed a significant anthelmintic effect ($p \leq 0.05$) by mortality and temporary paralysis of live *H. contortus*. *ZSC* leaves extract at the doses of 100 mg/kg and 400 mg/kg reported 61.5% and 78.7% reduction in percent of egg count in the feces (Intisar et al. 2015).

2.4.13 Hepatoprotective Activity of *ZSC*

Hepatoprotective effects against carbon tetrachloride (CCl_4)-induced liver injury is exhibited by the methanol and aqueous extract of leaves of *ZSC*. It also decreased the serum creatinine and uric acid level and enhanced protein depletion in kidney tissue with a significant reduction of MDA concentration. All the biochemical markers related with hepatic injury showed beneficial values after treatment with the extract (Al-Ghamdi et al. 2018). Aqueous extract of *ZSC* leaves showed effective results against CCl_4-induced hepatic fibrosis. The results of histopathological, biochemical, and histology texture analyses displayed that *ZSC* significantly hinder the progression of hepatic fibrosis with marked reduction in the activities of serum ALT and AST. *ZSC* aqueous leaves extract also reduced the expression of a-smooth muscle actin and the deposition of types I and III collagen in CCl_4-injured rats (Amin and Ghoneim 2009). The hepatoprotective effect of the *ZSC* fruits as an antioxidant against CCl_4-induced oxidative stress and hepatotoxicity in rats indicated that *ZSC*F restored normal levels of malondialdehyde and retained control activities of endogenous antioxidants such as superoxide dismutase (SOD) and glutathione peroxidase (GSH) (Yossef et al. 2011). The ameliorative role of *ZSC* leaves extracts against hepatic injury induced by *Plasmodium chabaudi*-infected erythrocytes has been related with its effect on oxidative marker in the infected liver tissues (Hafiz et al. 2019).

2.4.14 Antiplasmodial Activity of *ZSC*

ZSC is extensively used as traditional medicine in malaria endemic regions (Adzu et al. 2007a, b). *ZSC* leaves extract exerts its action against *Plasmodium* infection by significant restoration of hepatic oxidative markers, restoration of hemoglobin level and erythrocyte counts, as well as a reduction in the inflammatory cell count. Experimental mice infected with *P. chabaudi* showed infected erythrocytes, inflammatory cell infiltration, increased number of van Kupffer cells, and hepatocyte vacuolation. *ZSC* leaves extract treatment showed significant reduction in the level of mean corpuscular hemoglobin (MCH) and other pathological issues (Hafiz et al. 2019). *ZSC* showed significant beneficial effect on *P. berghei* parasite-induced hepatic and spleen tissue damage (Hafiz and Mubaraki 2016). *ZSC* leaves extract was able to significantly reduce the parasitemia level (Mishra and Bhatia 2014). *ZSC* leaves extract showed significant amelioration in the signs of inflammatory cell infiltration and hepatocyte vacuolation in the liver of infected mice with *P. berghei* (Hafiz and Mubaraki 2016). *ZSC* extracts have eloquent effects on hepatic tissues and have been evident from the histopathological pictures of the liver, kidney, and spleen affected by *Schistosoma* infection (Ali and Hamed 2006). Antitrypanosomal and antiplasmodial activity of *ZSC* leaves extract from Sudan was evaluated by in vitro assays. Methanolic extracts of leaves showed antiplasmodial activity against a chloroquine-sensitive strain of *P. falciparum* NF54, whereas the antitrypanosomal activity was evaluated against *Trypanosoma brucei rhodesiense* STI900 (African strain), and the results confirmed its traditional claim (Mohamed et al. 2017). *ZSC* chloroform fraction of root bark is a potential antiplasmodial agent against the *P. berghei*, justifying its folkloric usage as an antimalarial (Al-Said 1993). *ZSC* leaves extract has the ability to restore the normal levels of MDA in *Schistosoma mansoni*-infected mice (El-Rigal et al. 2006). From these scientific reports, it is evident that *ZSC* may be a source of potential chemotherapeutic antimalarial agent.

2.4.15 *ZSC* in Skin Diseases

The traditional claim of anti-inflammatory, soothing, and antibacterial activity of the *Ziziphus* tree represents a possible treatment option of the rash particularly in patients on EGFR blockers. A 50-year-old patient with a lung cancer developed a papulopustular rash after administering erlotinib. He treated himself with *ZSC* minced leaves, and he reported that his rash disappeared completely. Based on this clinical case report, a phase I trial of *Ziziphus* cream is undergoing which includes all patients on EGFR blockers. This study will help to discover a potential prevention and cure of the troublesome skin rash, and also it authorizes the clinical use of *ZSC* (Alzahrani et al. 2019).

2.4.16 Osteogenic Activity of *ZSC*

Administration of *ZSC* leaves extract to diabetic rats showed reduction of serum parathyroid hormone (PTH) with increased levels of CT which may have an association to enhanced bone mineralization and bone formation, probably due to presence of numerous types of flavonoids. Significant changes in PTH and bone tartrate-resistant acid phosphatase (TRAP) were observed along with decreases in serum calcitonin (sCT), procollagen type 1 (PC1), and osteocalcin (OC). In both serum and bone, there is a reduction in bone alkaline phosphatase (BALP), bone mineral density (BMD), and levels of Ca and P. Administration of *ZSC* leaves extract was helpful in reducing body weight loss and all diabetes-related bone changes followed by increasing IGF-1 bioavailability (El-Wakf et al. 2017).

2.4.17 Hypolipidemic Activity of *ZSC*

The antihyperlipidemic activity of *ZSC* could be attributed to inhibition of oxidative stress by phenolic compounds (El Rabey et al. 2014; Al-Sieni et al. 2020). *ZSC* leaves powder at the dose of 500 mg/kg body weight orally administered to hypercholesterolemic male rats showed improvement in the biochemical blood tests and the histology of the studied organs tissues. The concurrent treatment with *ZSC* seed aqueous extract in hypercholesterolemic rats showed reduction in the oxidative stress and restored the altered histological features to normal, and this could be related to the effect of phenolic compounds (Al-Sieni et al. 2020). *ZSC* leaves extract effectively reduced hyperlipidemia, lipid peroxidation, and activity of liver enzymes. The hypolipidemic effect of *ZSC* leaves extract is primarily due to its phenol constituents which inhibit oxidative stress (Parsaeyan and Rezwani 2014).

2.5 Patents Granted to *ZSC*

ZSC is considered as a good source of triterpenic acid, saponins, and flavonoid glycosides. It is quite popular for its folkloric use as a shampoo and in the treatment of skin diseases. Ghomi in 1998 obtained a patent for the *ZSC* formulation which was claimed to reverse the hair graying and was effective in treating psoriasis. It was claimed in the invention that the dried leaves extract of *ZSC* could be used to reduce skin inflammation and treat sunburn, nonspecific erythema, and itching. *ZSC* extract exerts cooling effect on skin and therefore is desirable to use as skin cleansers for sensitive skin. The extract is also effective as excortication agent (Ghomi 1998).

Mukherjee et al. (2006) developed an herbal-based formulation exhibiting broad-spectrum anticancer activity. The herbal preparation containing *Zizyphus* extract, rich in betulinic acid, was shown to inhibit protein kinase C activity of cancer cells and induce apoptosis (Mukherjee et al. 2006). Krasutsky et al. (2006) patented an azeotropic distillation method for the isolation of natural products such as betulin, lupeol, and/or betulinic acid in high yield (Krasutsky et al. 2006). A summary of few

Table 2.4 Patents granted to *ZSC*

S no	Patent no and year	Inventors	Invention title
1.	US5849302A 1998-12-15	MS Ghomi	Medicaments and cosmetics comprising *Zizyphus spina-christi* extracts
2.	US20060159783A1 United States 2006-07-20	R Mukherjee D Khattar M Jaggi A Singh M Kumar H Bala	Method for treating cancer using betulinic acid-rich herbal extract
3.	EP1687326A2 2006-08-09	PA Krasutsky O Kolomitsyna DA Krasutskyy OD Kacharov IV Kolomitsyn	Method for obtaining natural products from plant material

important patents granted to *ZSC* for its use in cosmetic and pharmaceutical industries is presented in Table 2.4.

2.6 *ZSC* in Nanotechnology

In the past decade, plant extracts and the natural products have been widely used for the synthesis of an array of metal nanoparticles (Haris et al. 2017). This shift in the paradigm from traditional chemical methods to green biosynthesis of nanoparticles is partly due to the cost-effective and environmental friendly method offered by the naturally occurring plant products. Medicinal plants contain diverse nature of secondary plant metabolites such as flavonoids, terpenoids, tannins, phenolic acids, and alkaloids, which act as reducing as well as capping agents for the synthesis of nanoparticles (AbuKhader and Khan 2017; Zayed et al. 2015). *ZSC* being rich in polyphenolic compounds have also been explored as an alternative source of biosynthesis of metal nanoparticles.

Zayed et al. (2015) used the *ZSC* leaves extract as a reducing and capping agent at the room temperature to synthesize Ag nanoparticles (AgNPs) via a single-step, rapid, cost-effective, and eco-friendly biosynthetic method. The nanoparticles were found to be spherical in shape with a uniform size distribution (average particle size diameter 19 nm). IR studies indicated the presence of hydroxyl, amino, carbonyl, and amide functionalities in the plant extract which could be responsible for the reduction and/or stabilizing the developed nanoparticles. The *ZSC*-stabilized AgNPs displayed an excellent catalytic activity and efficiently reduced 4-nitrophenol into 4-aminophenol (Zayed et al. 2015). AgNPs synthesized using aqueous leaves extract of *ZSC* have been shown to exhibit potent antibacterial activity against *S. aureus*, *Acinetobacter* sp., *P. aeruginosa*, and *E. coli*. These nanoparticles when loaded on band aids also showed excellent antibacterial effect against multidrug-resistant bacteria (Halawani 2017).

A study also reported the reliable antifungal activity of AgNPs synthesized using *ZSC* leaves extract against pathogenic fungal isolates *A. niger*, *A. flavus*, *P. digitatum*, and *F. oxysporum* (Abdelkader et al. 2019). Khani et al. (2018) used fruit extracts of *ZSC* for the green synthesis of copper nanoparticles (CuNPs). The CuNPs exhibited good antibacterial activity and were shown to act as an efficient adsorptive nanomaterial which was able to remove 95% of crystal violet (CV) dye from aqueous solution at optimized conditions (Khani et al. 2018).

2.7 *ZSC* as an Adsorbent to Remove Manganese from Aqueous Solution

Activated carbon from the *ZSC* seeds possesses good adsorption properties and has the ability to remove manganese metal from the water. The adsorption capacity of *ZSC* activated carbon is better than the natural zeolitic tuff, pecan nutshell biosorbent, *Pithecellobium dulce* carbon, and crab shell particles (Omri and Benzina 2012).

2.8 *ZSC* Toxicity

The scientific reports of *Ziziphus* species hold numerous gaps that need thorough exploration especially for biological activity and toxicity. Pharmacological activities of *ZSC* have been considered extensively, but there is a scarcity of the available scientific reports/data on the toxicity associated with the consumption of the various parts of the *ZSC* plant, although *ZSC* fruits and leaves appear to be safe as indicated by the relatively high LD_{50} values in experimental animals (Abdel-Zaher et al. 2005). Shah et al. (1989) reported that *ZSC* leaves extract did not produce acute toxicity in the animals but higher doses led to decreased locomotor activity. Swiss albino mice did not show any signs of toxicity, and also no mortality was observed even after the chronic treatment for 3 months (Shah et al. 1989). Similarly, Abdel-Zaher et al. (2005) did not observe any signs of hepatotoxicity and nephrotoxicity in rats upon chronic oral administration of the butanol extract of *ZSC* leaves (Abdel-Zaher et al. 2005). *ZSC* methanolic leaves extract had a markedly protective effect against aflatoxicosis, and it significantly improved all biochemical parameters and histological profiles of the liver, kidney, and testis of tested rats (Abdel-Wahhab et al. 2007). The acute toxicity/safety of the hexane root bark extract of *ZSC* in mice with the experimental doses of 25, 50, and 100 mg/kg reported LD_{50} of 871.78 mg/kg for intraperitoneal administration and clinched the safety limit of the *ZSC* (Adzu et al. 2008). In addition, the oral LD_{50} of the butanol extract of *ZSC* leaves in mice was 3820 mg/kg (Abdel-Zaher et al. 2005). Aliquots of the concentrated *ZSC* juice (fruits and leaves) were used to assess the safety limits of the phenolic compounds. LFT and RFT reports portrayed that the administration of *ZSC* juice did not cause any changes in liver and kidney functions. On the contrary, BHT at 200 ppm induced significant increases in the enzyme activities and the serum levels of total lipids, uric

acid, and creatinine (Amany et al. 2013). Abubakar et al. (2018) carried out first toxicity study by oral administration of 5000 mg/kg of *ZSC* hydro-methanolic fruit extract and recorded zero mortality rate proving its safety (Abubakar et al. 2018). The acute toxicity study of single dose of *ZSC* leaves methanolic extract (2000 mg/kg per oral) in adult male mice did not reveal any sign of toxicity or mortality during 2 weeks observation period. Furthermore, there were no significant changes in the mean body weight or absolute weight of the liver, kidney, spleen, or heart, indicating high safety of the extract (Dkhil et al. 2018a, b). *ZSC* leaves extract 300 mg/kg *ZSC* leaves extract depicted protective role in $HgCl_2$-induced nephrotoxicity and by acting on Kim-1 expression, lipid peroxidation, and nitric oxide production; suppression of the Nrf2-antioxidant response pathway; upregulation of IL1β, TNFα, and NOS2; and potentiation of proapoptotic activity. *ZSC* leaves extract has the ability to produce beneficial effects against mercury-induced renal toxicity (Almeer et al. 2019). These effects resulted from its chelation and antioxidant, anti-inflammatory, and antiapoptotic activities. *ZSC* minimized the pathological effect produced by mercury in the renal tissue, and also it enhanced Hg clearance and reduced its accumulation. *ZSC* leaves extract successfully inhibited the Kim-1expression induced by Hg exposure (Dkhil et al. 2018a, b). Upregulation of Nfe2l2, Hmox1 expression, and protection against Hg-induced oxidative stress in renal tissue were also supported by *ZSC*. *ZSC* leaves extract boosted Nfe2l2 and Hmox1 expression in an ulcerative colitis rat model. The antiapoptotic activity of *ZSC* leaves extract is mainly due to its ability to appease ROS, as mentioned by several studies (Almeer et al. 2018; Dkhil et al. 2018a, b; Singh et al. 2012).

Contrary to the above findings, a recent study conducted by Owolarafe et al. (2020) cautioned against the indiscriminate use of leaves. Owolarafe et al. (2020) investigated the hematological and hepatorenal toxicities of the aqueous methanol extracts of seeds of *ZSC* in Wistar albino rats. The seed extracts upon oral administration to rats at 200, 600, and 1000 mg/kg body weight for 2 weeks were found to cause hepatic vascular congestion and fibrosis at 600 and 1000 mg/kg body weight with no visible histoarchitectural effect on the kidney. Seed extract was noted to significantly ($P < 0.05$) reduce the levels of white blood cells, neutrophils, SGOT, chloride, urea, and creatinine and increase the levels of lymphocytes, platelets, direct and total bilirubin, albumin, SGPT, alkaline phosphatase (ALKP), SGOT, serum calcium, creatinine, urea, and organ-body weight ratios (Owolarafe et al. 2020).

2.9 Conclusion and Future Directives

It is perceptible that *ZSC* is a valuable medicinal resource encompassing phytoconstituents of diverse chemical classes with wide spectrum of pharmacological uses. The plant is traditionally considered as a safe herbal medicine. Its fruits are edible and widely consumed by the people in the gulf region. The contemporary congregate information shows that alkaloids, flavonoids, and saponin glycosides such as christinin A might be useful in the development of new drugs to treat various acute and chronic ailments. The limited preclinical and clinical reports available to

support the safety in different populations are still a question which severely limits the diversity of research and industrial application of *ZSC* in the medical field. Cyclopeptide alkaloids are the main phytoconstituents present in this plant species, and therefore the possible hepatorenal toxicity should not be ignored.

It is evident that *ZSC* possesses broad-spectrum antimicrobial property, and this might be helpful in the management of the new life-threatening diseases including COVID-19. Extensive pharmacological and chemical experiments integrating human clinical studies investigating inter- and intracellular metabolic pathways should be a focus in future. Isolation of bioactive molecules from *ZSC* might act as a good lead that can be employed in novel therapeutic formulation based on an increasing attention toward green chemistry and transitional medicinal plants in recent years. Utilization of medicinal plants for novel drug delivery applications has better stakes of being sustainable with potential medical and commercial impacts in the coming decades. *ZSC* has vast untapped therapeutic applications yet to be revealed and explored with a complementary blend of skills and expertise in the field of phytochemistry, pharmaceutics, and pharmacology.

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Traditional Uses, Phytochemistry, and Pharmacological Profile of *Salvadora persica* Linn

3

Tanveer Alam, Shah Alam Khan, and U. M. Dhanalekshmi

Abstract

Salvadora persica Linn. (chewing stick) is a desert plant that belongs to the family Salvadoraceae. Parts of this plant have been used as a toothbrush for centuries particularly in the Arab world. It is a highly branched and small evergreen tree or a big shrub that resembles Indian species growing in the hot and arid weather. The ripened berries of *Salvadora persica* are peppery but edible. The berries are eaten fresh as carminative and appetite stimulant. The World Health Organization has recommended using *Salvadora persica* as chewing sticks for tooth cleaning purpose. This plant has been known to possess wide spectrum of biological and therapeutic activities. Numerous studies have provided scientific evidence of its usefulness in the treatment of plaques, convulsions, infertility, rheumatism, biliousness, and bacterial and fungal infections. It is also used traditionally as analgesic, cytotoxic, carminative, diuretic, and astringent. This chapter aims to provide an insight on the traditional uses, the pharmacologic actions, and therapeutic benefits of *Salvadora persica* with a comprehensive explanation of various phytochemicals isolated from different parts of the plant.

Keywords

Salvadora persica · Chewing stick · Phytochemistry · Traditional uses · Edible

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Abbreviations

ABTS	2,2-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) assay
ACE	Angiotensin-converting enzyme
ASA	Acetylsalicylic acid
BHA	Butylated hydroxyanisole
BITC	Benzyl isothiocyanate
bw	Body weight
CHX	Chlorhexidine
CMC	Carboxymethylcellulose
CV	Crystal violet
DEAE	Sepharose-diethylaminoethanol polymer
DPPH	2,2-Diphenyl-1-picrylhydrazyl assay
FAME	Fatty acid methyl ester
FRAP	Ferric reducing antioxidant power assay
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
HCTZ	Hydrochlorothiazide
HDL	High-density lipoproteins
i.p.	Intraperitoneal
IC_{50}	Inhibitory concentration in 50% of population
IRI	Immunoreactive insulin
LDH	Lactic dehydrogenase
LDL	Low-density lipoproteins
MCF7	Michigan Cancer Foundation-7
MDR	Multidrug resistant
MEO	Miswak essential oil
OVX	Ovariectomized
po	Per oral
PTZ	Pentylenetetrazol
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SPB	Sodium pentobarbital
TC	Total cholesterol
TG	Triglycerides
UAE	United Arabic Emirates
WHO	World Health Organization

3.1 Introduction

Salvadora persica (*S. persica*) is a desert plant belonging to the family Salvadoraceae. The roots and branches of the tree are used as tooth cleaning sticks since ancient times in several developing countries and hence the name toothbrush

tree, chewing stick, or miswak. Muslims around the world use roots and twigs of this plant for teeth cleaning prior to the prayers. A number of research studies have demonstrated the protective effect of *S. persica* in tooth decay. It is a desert plant that can survive in the extreme harsh weathers such as very hot climate to salty soils. The plant can grow in a dry, barren *region*, where sandy or rocky soil is available (Haque and Alsareii 2015). The plant can also grow on clay, loam, sand, and black soils. Several geographical variations have been observed in many countries that could be attributed to several factors including source of water, soil properties, climatic changes, and anthropogenic effects (Anthony and Timothy 2015).

S. persica is a highly branched, big shrub or a small tree commonly grown in the Middle East, South Asia, and few of North African countries (Wu et al. 2001). There are around 182 species in the family, and among all *S. persica* is the most extensively used species. The use of *S. persica* toothbrush is very prevalent throughout the world because of religious and traditional links, high availability, and economic values (Almas 1993). The World Health Organization (WHO) recognized the importance of miswak in maintaining oral hygiene and therefore recommended its regular use to keep mouth clean and free from dental problems (WHO 1984). The use of miswak is widespread in most of the Middle East and some Asian and African countries with large Muslim population owing to the religious belief, culture, and its beneficial effects on dental hygiene (Hardie and Ahmad 1995; Wu et al. 2001). Historical records indicate that during the Babylonian civilization (the Greek and Romans, around 7000 years ago), *S. persica* toothbrush was used for dental hygiene. The application of chewing sticks for cleaning teeth remains to be an important part of their daily life in several Afro-Asian communities (Almas 2002; Niazi et al. 2016). The fact that Islam has embraced oral cleanliness as a component of religious practice and especially encourages miswak for this reason, as well as the fact that it has been documented since ancient times, has contributed to miswak's greater popularity (Saeed 1988; Ra'ed et al. 1999).

3.2 Botanical Description

S. persica is a small tree or evergreen shrub having several branches. It can grow up to 6–7 m (20–30 ft) in height. Branches are white in color at first becoming gray and rough on trunks and then erect, pendulous or trailing, glabrous or pubescent (Fig. 3.1).

3.2.1 Stem Bark

It has a grayish black bark that is channeled when young. It comes in 15–25 cm length and 10–15 cm wide parts. Presence of vertical lenticels and longitudinal fissures makes bark scabrous and cracked. The tint of the dry bark changes to black with time.

Fig. 3.1 Pictures of different parts of *S. persica* Linn. plant. (Pictures taken by Mr. Ghanim Salim Aalthani, UoN, Nizwa, Oman)

3.2.2 Leaves

The leaves are glaucous dark green measuring 6.0–10 cm long and 3.0–5.0 cm wide. Leaves are succulent, leathery and thick textured, opposite, oblong-elliptic to circular in shape. Petioles are glabrous and 1.0 cm long.

3.2.3 Flowers

Flowers are very small, greenish to yellowish in color. Flowers are 5–12.5 cm long. Pedicels are 0.15–0.3 cm long and glabrous. Calyx is 0.12 cm long, glabrous with rounded lobes. Corolla is almost double in size as calyx. Stamens are 4 in number, shorter than corolla, and exerted. Ovary bilocular or unilocular, erect ovule in each locule and stigma sessile and bilobed.

3.2.4 Fruits and Seeds

Fruits are round in shape with a single seed berry, juicy, but pungent. Fruits upon maturing change their color from pink to purple-red and appear in clusters. Seeds are 1.4 mm in diameter, smooth, and brown.

3.3 Edible Parts

Leaves: Leaves can be used as a salad or cooked as a sauce or green vegetable.

Fruits (Berries): The berries are edible once they have ripened to dark red.
Seeds: Seed oil is also edible.

3.4 Taxonomical Classification

Dr. Laurent Garcin coined the word Salvadora in 1749 to honor a Barcelona pharmacist, J. S. Bosca (1598–1681). The *persica* word is used to symbolize Persia (Ahmad and Rajagopal 2013). The taxonomical classification of *S. persica* plant is presented in Table 3.1.

3.5 Traditional Uses

Several studies have reported that different parts of *S. persica* are used traditionally to treat splenalgia, asthma, bronchitis, cough, verminosis and hemorrhoids blisters, scorpion bite, flatulence, and helminthiasis. The roots and shoot sticks are used as tooth brushes for centuries in many parts of the world. The underground parts (roots) of *S. persica* are used as toothbrushes in the United Arab Emirates (UAE), and the crushed leaves are mixed with oil to alleviate joint and knee ailments (http://www.motherherbs.com/salvadora-persica.html). Interestingly, miswak has been used for medicinal purposes by several communities, mostly in Asian and African continent. Some of the most common folkloric uses of *S. persica* are described in Table 3.2.

Table 3.1 Taxonomic hierarchy of *S. persica* Linn

Taxonomic hierarchy	
Rank	Scientific name and common name
Kingdom	Plantae–plants
Subkingdom	Viridiplantae
Infrakingdom	Streptophyta–land plants
Superdivision	Embryophyta–seed plants
Division	Tracheophyta
Subdivision	Spermatophytina
Class	Magnoliopsida
Subclass	Rosidae
Order	Brassicales
Family	Salvadoraceae
Genus	*Salvadora*
Species	*persica*
Binomial name: *Salvadora persica* (Khari Jaal), *Salvadora oleoides* (MeethiJaal)	

Table 3.2 Traditional uses of *S. persica* Linn. plant

Country	Part used	Mode of preparation	Ailments/medicinal uses	References
India	Leaf	Leaves are heated and tied up in thin cotton cloth and then applied Crude juice of leaves	Rheumatism Scurvy	Parveen et al. (2007)
		Paste	Rheumatism, scurvy	Patel and Patel (2017)
		Paste of 8–10 crushed leaves is taken po with water	Constipation	Katewa et al. (2004)
		Decoction, 25 mL twice daily po	Asthma, expectorant	Savithramma et al. (2007) and Rabari (2016)
		Juice of leaves is applied externally to the affected area	Body pain, scabies, leukoderma	Kosalge and Fursule (2009) and Mali and Bhadane (2011)
		Not reported	Diabetes	Gunasekaran and Balasubramanian (2012)
	Leaf, fruit	Paste	Boils, swelling, piles, constipation, indigestion	Kumhar et al. (2017)
	Fruit	Not reported	Purgative	Rabari (2016)
	Root Bark	Paste is applied locally	Blisters	Katewa et al. (2004)
		Ground with mustard oil and bandaged on swelling	Gout	Bharti (2015)
		Fresh powder	Arthritis	Patel et al. (2013b)
		Decoction po	Fever	Patel and Patel (2017)
	Young root	As a toothbrush	Toothache	Patel et al. (2013b)
	Young branch and leaf	Powdered and mixed with honey, Boiled extract	Bronchitis Seasonal cough and cold	Patel et al. (2013b)
	Whole plant	Not reported	Toothache, skin	Patel et al. (2013a)
	Root, shoot, leaves, bark	Not reported	Snakebite treatment, rheumatism, tonic	Sathe et al. (2014)
	Fruit, seed oil	Not reported	Laxative, hemicrania, intestinal parasites,	Khare (2004)

(continued)

Table 3.2 (continued)

Country	Part used	Mode of preparation	Ailments/medicinal uses	References
			urinary disorders, suppurating skin diseases	
	Fresh fruit	Taken with buttermilk	Piles	
Pakistan	Root, soft bark, leaf, fruit, Seed	Toothbrush, ash, powder, extract, decoction	Toothache, skin allergy, constipation, painkiller, GIT worms, jaundice	Yaseen et al. (2015)
	Leaf	Decoction of leaves are used for vomiting	Malaria symptoms	Shah and Rahim (2017)
Jordan	Branch	Not reported	Cleansing and disinfecting teeth, gums	Lev and Amar (2002)
	Stem	Brushing	Cleansing and disinfecting teeth, gums	Alzweiri et al. (2011)
Saudi Arabia	Leaf, root	Decoction	Mouthwash, to cure tooth/gum problems, and as a remedy for joint pain	Sher and Alyemeni (2011) and Sher et al. (2011)
	Root	Decoction	Epilepsy, gonorrhea, skin diseases, spleen troubles, stomach ulcer	
	Seed	Not reported	Seed oil is used to treat skin inflammation and rheumatism	
Kenya	Root, stem	Not reported	Eye infections, worms, malaria, stomach ache, constipation, tonic, cold, teeth hygiene, respiratory infections	Kimondo et al. (2015)
	Root	Boil and drink	Stomach upset	Fratkin (1996)
		Not reported	Helminthiasis	Muthee et al. (2011)
		Grinded/crushed root soaked in water	Flu/common cold Stomachache	Kiringe (2006)
		Grinded/crushed root soaked in water with some salt and little milk	Typhoid Malaria	
	Not reported	Not reported	Dental caries, relieve tooth ache and gum disease	Ngaruiya (2015)
	Root, fruit	Not reported	Malaria, gonorrhea, common cold	Tsigemelak et al. (2016)

(continued)

Table 3.2 (continued)

Country	Part used	Mode of preparation	Ailments/medicinal uses	References
	Root, stem bark	Boiled and taken as infusion	Chronic joint pains	Wambugu et al. (2011)
	Leaf	Infusion in hot water	Veterinary: Rinderpest	Bizimana (1994)
	Whole plant	Ashes mixed in water and given orally	Veterinary: Diarrhea	Bizimana (1994)
	Root	Ashes from the root are mixed in water and given orally	Veterinary: Trypanosomiasis	Bizimana (1994)
		Root soaked in water for many hours and given to cows orally	Veterinary: Retained afterbirth	Bizimana (1994)
Mali	Leaf	Decoction of fresh leaves	Influenza	Hope (2005)
		Porridge of crushed fresh leaves	Cold and cough	
	Not reported	Extract is used for bathing	Malaria	Diallo (2011)
Tanzania	Root bark	Paste of root powder with oil Topical use–applied locally in the mouth. The powdered root bark is added to porridge	Oral candidiasis	Runyoro et al. (2006)
	Root	Decoction po	Female sterility treatment	Chhabra et al. (1991)
Namibia	Bark, stem	Bark and stems are crushed, soaked in water Topically applied to treat skin infections in goats	Livestock diseases	Chinsembu et al. (2014)
Ethiopia	Root	Crushed/decoction or boiled with goat meat po	Chest pain, boils, abscess, tuberculosis, cough with blood, flu, antipyretic, malaria, cancerous swelling	Teklehaymanot and Giday (2010)
	Leaf	Leaves are powdered, boiled, and drunk after adding sugar	Malaria	Mesfin et al. (2012)
Egypt	Leaf, fruit, branch	Infusion of the leaves and fruits	Analgesic	Eissa et al. (2014)
		Young branches chewed	Toothache	
	Leaf	Infusion	Urinary retention, bilharzia	Goodman and Hobbs (1988)

(continued)

Table 3.2 (continued)

Country	Part used	Mode of preparation	Ailments/medicinal uses	References
	Root, branch, leaf, fruit	Not reported	Tooth brush and mouth antiseptic, urinary tract pain, diuretic	Mahmoud and Gairola (2013)
Eritrea	Leaf, twig	Crushed fresh leaf po	Fever, gonorrhea, and bronchial asthma	Ogbazghi and Bein (2006)
	Root	Used as chewing sticks	Dental care	
Somalia	Fresh wood	Crushed wood with water po	Against hepatomegaly caused by malaria	Samuelsson et al. (1993)
	Fresh rootbark	Powdered roots with water applied topically	Against furuncles	
	Fresh or dried root	Powdered root with fresh or fermented cow milk po	Against dysmenorrhea	
Senegal	Root	Not reported	Diuretic, Blackwater fever, rheumatism, venereal diseases	Oliver-Bever (1986)
Sudan	Bark	Powdered bark paste mixed with water	In cases of serious febrile diseases	Oliver-Bever (1986)
	Dried leaf	Not reported	Flatulent dyspepsia	
East Africa	Root, bark	Not reported	Livestock diseases	Katerere and Luseba (2010)
West Africa	Twig	Salt residue	Veterinary: Abdominal disorders	Bizimana (1994)
Sub Saharan Africa	Root	Root decoction with water	Ethnoveterinary: Brucellosis Ethno veterinary: Retained afterbirth	Toyang et al. (2007)

3.6 Pharmacological Activities

Since prehistoric times, medicinal plants and their chemical constituents have been used by humankind to alleviate their suffering. A large number of currently used drugs in clinical practice have been derived from plants. Plant-based drugs especially those which are used as traditional medicine comprise one of key strategies in drug discovery and development. Therefore, the scientific community including herbal industries has paid a considerable attention to evaluate the potential, efficacy, and safety of plant-based drugs primarily used as the traditional or ethnomedicine. The findings of the researchers' experimental pharmacological investigations on *S. persica* are summarized in Fig. 3.2. It is evident that extracts of varying polarities

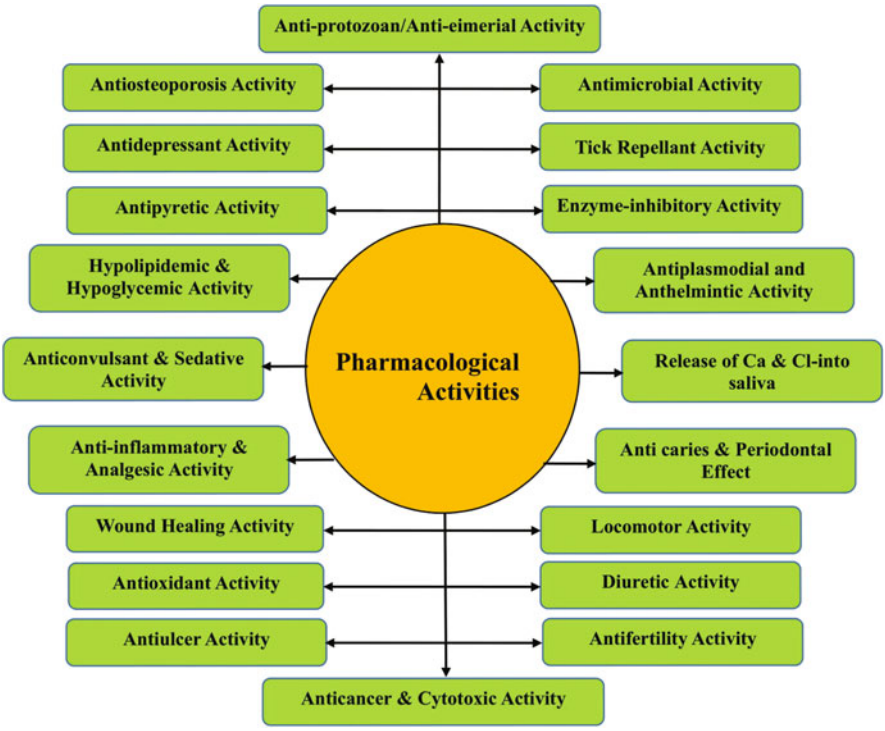

Fig. 3.2 Pharmacological uses of *S. persica* Linn. plant

and individual phytochemicals extracted from *S. persica* plant clearly have distinct biological actions. Adaptogenic effects, namely, hepatoprotective, hypoglycemic, antioxidant, antiplaque, antifungal, antipyretic, antiulcer, hypolipidemic, and anticonvulsant effects, are prominent in this plant. Furthermore, phytoconstituents such as trimethylamine $(CH_3)_3N$) and salvadorine have been shown to exhibit promising activities including antibacterial, antiphlogistic, and gingiva-stimulating properties. Pharmacological activities of the phytoconstituents isolated from *S. persica* are presented in Table 3.3.

3.6.1 Antimicrobial Activity

Various investigations have demonstrated *S. persica's* broad-spectrum antimicrobial activity against bacterial, fungal, and viral infections. However, findings of these studies clearly indicated a dose-dependent variation in the microorganisms' susceptibility. The antimicrobial activity of *S. persica* and its extracts is summarized in Table 3.4.

Table 3.3 Phytoconstituents of *S. persica* possessing biological activities

S. no.	Components	Biological activity
1.	*Silica*	As an abrasive material to remove stains giving the teeth whiteness (El-Mostehy et al. 1983)
2.	*Tannins* (tannic acid)	Reduces the clinically detectable gingivitis (Chawla 1983); help in reducing plaque and gingivitis (Kubota et al. 1988)
3.	*Resins*	Forms a layer over the enamel and thus protects against caries
4.	*Alkaloids* (salvadorine)	Bactericidal effect and stimulatory action on the gingival (Almas 1993)
5.	*Essential* (*volatile*) *oils*	Exert carminative, antiseptic action (El-Mostehy et al. 1983). Their mild bitter taste stimulates the flow of saliva, which is antiseptic (Dorner 1981)
6.	*Sulfur*	Its pungent taste and smell have a bactericidal effect (Grant 1990)
7.	*Vitamin C*	Antioxidant and helps in the healing and repair of tissues (George and William 1985)
8.	*Sodium bicarbonate* (baking soda) $NaHCO_3$	Used as dentifrice and having a mild germicidal action (Abo Al-Samh and Al-Bagieh 1996)
9.	*Chloride*	Its high concentration inhibits calculus formation and helps in removing stains from the teeth (Farooqi and Srivastava 1968; El-Mostehy et al. 1983)
10.	*Calcium*	With saliva it inhibits demineralization and promotes remineralization of tooth enamel (Kubota et al. 1988)
11.	*Benzyl nitrate and benzyl isothiocyanate* (BIT)	Act as chemo-preventive agents (Ezmirly and El-Naser 1981), virucidal (Al-Bagieh and Weinberg 1988), antibacterial, and anti-fungal agents (Brown and Jacobs 1979; Al-Bagieh 1992)
12.	*Butanediamide, ~ N4-bis (phenylmethyl)-2(S)-hydroxy-butanediamide*	Antimicrobial agent against Gram-positive and Gram-negative bacteria (Khalil 2006)
13.	*N-benzyl-2-phenylacetamide*	Inhibitory effect on human collagen-induced platelet aggregation and a moderate antibacterial activity against *Escherichia coli* (Khalil 2006)
14.	*Trimethylamine*	Decreasing plaque accumulation, antibacterial, and antiphlogistic (Hattab 1997)
15.	*Fluoride*	Anti-decay effects (Chawla 1983)
16.	*Persicaline*	Antioxidant activity (Farag et al. 2018)
17.	*β-Amyrin*	Calcium oxalate urolithiasis activity (Geetha et al. 2010)

Table 3.4 Antimicrobial activity of *S. persica* Linn. plant

Plant parts/ extracts	Microorganisms used	Results	References
Aqueous and methanol extracts of miswak	*S. aureus*, *St. mutans*, *S. faecalis*, *S. pyogenes*, *P. aeruginosa*, *C. albicans*, *L. acidophilus*	Aq. extract was most potent against *S. faecalis.* Both extracts had equal antifungal activity against *C. albicans*	Firas et al. (2008)
Miswak pieces without extraction	*St. mutans*, *L. acidophilus*, *A. actinomycetemcomitans*, *P. gingivalis*, *H. influenza*	Highly effective against *P. gingivalis*, *A. actinomycetemcomitans*, and *H. influenzae*	Sofrata et al. (2008)
Miswak toothpaste	Dental plaque bacteria	Significant antibacterial effect than placebo	Poureslami et al. (2007)
Methanol, chloroform, and aqueous extract of miswak	*A. flavus*, *A. fumigates*, *A. niger*, *C. albicans*	Significant antifungal activity in comparison to clotrimazole	Abdalmoniem and Saadabum (2006)
Aqueous extracts of miswak	Cariogenic bacteria	Bacteriostatic effect	Darmani et al. (2006)
Aqueous extract of chewing stick	*S. faecalis*, *S. pyogenes*, *S. mutans*, *C. albicans*, *S. aureus*, *S. epidermidis*	Highly effective against *S. faecalis* but was mildly effective against *S. mutans*	Almas et al. (2005)
Aqueous extract of twigs	*S. mutans*	Bacteriostatic effect	Hammad and Salla (2005)
Volatile oil of the leaves	*S. aureus*, *E. coli*, *P. vulgaris*, *S. mutans*, *K. pneumoniae*	Bacteriostatic effect	Al-Ali and Al-Lafi (2003)
Crude miswak extract	*C. albicans*, *S. mutans*, *A. actinomycetemcomitans*, *L. acidophilus*, *A. naeslundii*, *P. gingivalis*	Bacteriostatic effect	Abdel Rahman et al. (2002)
Aqueous extract of chewing sticks	*S. faecalis*, *S. mutans*, *S. aureus*, *C. albicans*	Effective against *S. faecalis* at 50% concentration	Almas (2001)
Bark, pulp, and whole miswak extracts	*S. faecalis*, *S. mutans*, *S. aureus*, *S. epidermidis*, *C. albicans*	Bark was effective against *S. feacalis* and *S. mutans.* Whole miswak was more effective compared with bark or pulp separately	Almas and Al-Bagieh (1999)
Aqueous extracts of Arak chewing stick	*S. mutans*, *S. faecalis*	Effective at 50% concentration on *S. mutans* and *S. faecalis*	Almas (1999)
Alcoholic extract of chewing stick	Aerobic and anaerobic bacteria from mouth canal of patients	Significant antimicrobial effect	Nawal et al. (2007)

(continued)

Table 3.4 (continued)

Plant parts/ extracts	Microorganisms used	Results	References
Oil constituent—Benzyl isothiocyanate	Oral pathogens and gram-negative bacteria	Rapid and strong bactericidal effect	Sofrata et al. (2011)
Methanol extract of stem	*H. pylori* from human duodenum	Bacteriostatic effect	Mirkamandar et al. (2012)
Root (in packing), root (without packing), and stem	Teeth isolates of *S. aureus*, *S. mutans*, and *C. albicans*	Packed and unpacked form root exhibited antimicrobial activity and stem did not show any activity	Naseem et al. (2014)
Aqueous, ethanol extracts of miswak	*S. mutans*, *L. acidophilus*, *E. coli*, *S. aureus*, *P. aeruginosa*	Ethanol extract was more effective	Mohammad (2013)
Ethanol extract of miswak	*S. aureus*, *E. coli*	Effective against *S. aureus*	Aljamali (2013)
Aqueous, ethanolic and hexane extracts of miswak	*E. coli*, *K. pneumoniae*, *S. enterica*, *E. cloacae*, *S. aureus*, *S. epidermidis*, and *B. flavum* and isolates of *S. xylosus*	Hexane extract showed significant antibacterial effect against all tested bacteria	Sellami et al. (2013)
Chewing stick	Gram-positive and gram-negative bacteria	Broad antimicrobial activity	Abhary and Al-Hazmi (2016)
Methanol extract of miswak	Isolated from saliva periodontitis: *S. aureus*, *S. mutans*, *C. albicans*	Effective antimicrobial activity	Al-Otaibi et al. (2018)
Injection of miswak extract	*E. faecalis*	91% isolates were eradicated	Monawer (2018)
Aqueous extracts of roots, twigs, and fruits	*S. pneumoniae*	Strong activity	Almaghrabi (2018)
Aqueous root extract	*A. niger*, *A flavus*, *A. fumigatus*	High concentration (100 mg/ml) of the root extract inhibited the growth	Saddiq and Alkinani (2019)
Methanol extract	*Staphylococcus*, *Streptococcus* sps.	Broad-spectrum activity	Khalil et al. (2019)
Aqueous fruit extract	Gram-positive, Gram-negative microorganisms *St. mutans* isolates	Selective antimicrobial activity for *Streptococcus mutans* isolates	Al Bratty et al. (2020)
Essential oil	*St. mutans*	Bacteriostatic effect	Khan et al. (2020)

(continued)

Table 3.4 (continued)

Plant parts/ extracts	Microorganisms used	Results	References
Hot and cold aqueous extracts of miswak	Mouth isolates of *S. aureus*, *C. albicans*	Cold aqueous extract is highly effective	El-Desoukey (2015)
Aqueous miswak extract	Saliva isolates of *S. mutans*, *Lactobacillus*	Bacteriostatic effect	Bhat et al. (2012)
Aqueous, methanol extracts of stem	*S. aureus*, *S. mutans*, *S. faecalis*, *S. pyogenes*, *L. acidophilus*, *P. aeruginosa*, and *C. albicans*	Aqueous extract inhibited all the microorganisms. Methanolic extract was resisted by *L. acidophilus* and *P. aeruginosa* but were less efficient than streptomycin	Al-Bayati and Sulaiman (2008)
Aqueous stem extract	*M. bovis*	Effective antimicrobial activity	Fallah et al. (2015)
Methanol, ethanol, and ethanol/ methanol extracts	*S. aureus* strain KKU-020, *E. faecalis*	Ethanol extract showed maximum activity against *E. faecalis*	Hesham and Alrumman (2014, 2016)
Ethanol-water (50:50) extracts of root	Oral pathogens: *A. viscosus*, *S. mutans*, *S. sobrinus*, *L. fermentum*, *Lactobacillus casei* subsp. *casei*, *E. corrodens*	Highly effective against *L. fermentum* and *A. viscosus* and least effective against *S. sobrinus*	Vahabi et al. (2011)
Ethanol extract of wood	Mouth isolate: *C. albicans*	Inhibited *C. albicans* growth	Pribadi et al. (2014)
Combined extract of stem and bark using petroleum ether, acetone, methanol, and water	*S. aureus*, *S. mutans*, *S. sanguinis*, *S. sobrinus*, *S. salivarius*, *L. acidophilus*, *C. albicans*	Methanol extract was more effective than the other extracts but was less effective compared to the positive control ofloxacin	Kumar et al. (2016)
Aqueous and ethanol extracts of stem	*S. enterica*, *P. vulgaris*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *B. cereus*, *S. epidermidis*, *S. aureus*	Aqueous extract showed greater activity against most of the tested organisms but was less effective against *S. enterica*. The antibacterial activity is better than penicillin G but lesser than gentamicin	Abdallah and Al-Harbi (2015)
Methanol and aqueous extract	*F. nucleatum*, *Lactobacillus casei*, *S. aureus*, *S. epidermidis*, *S. mutans*, *S. salivarius*	Exhibited potent antibacterial activity	Al-Sieni (2014)

(continued)

Table 3.4 (continued)

Plant parts/ extracts	Microorganisms used	Results	References
Acetone:water (80:20; v/v), ethyl acetate, and methanol extract of dry stems	*S. aureus*, *S. epidermidis*, *M. luteus*, *P. aeruginosa*, *S. typhimurium*, and *P. aeruginosa*; fungi: *C. albicans*, *C. dubliniensis*, *C. glabrata,* *C. parapsilosis*, *C. krusei*, *C. famata*, *C. kefyr*, *C. sake*, *C. holmii*, *C. lusitaniae*, *C. intermedia*, *C. atlantica*, *C. maritima*, *Pichia guilliermondii*, and *Pichia jardinii*	All the extracts showed bacteriostatic effect. The diluted acetone extract of *S. persica* showed significant antifungal activity	Noumi et al. (2011)
Stick	*E. faecalis*	Bacteriostatic effect	Al-Azzawi (2015)
Ethanol extract	*P. vulgaris*, *E. coli*, *Salmonella typhi*, *B. cereus*, *E. aerogenes*	Bacteriostatic effect against all the tested organism with *E. aerogenes* being the most susceptible	Anthony and Timothy (2015)
Ethanol (80%) extract of stick	*C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. krusei*, *C. parapsilosis*	Inhibitory activity against *all organisms*, whereas *C. krusei* was not susceptible	Naeini et al. (2014)
Ethanol extract of root	*C. albicans*, *E. faecalis*	Effective against *C. albicans* and is time dependent	Al-Obaida et al. (2010)
Miswak extract	*S. salivarius*, *S. sanguinis*, *Lactobacillus vulgaris*, *C. albicans*	Effective against all organisms but ineffective against *C. albicans*	Moeintaghavi et al. (2012)
Aqueous and methanol extracts of leaves	*S. aureus*, *E. coli*	Aqueous extract showed higher activity than methanol extract against *S. aureus*, but opposite effect was observed against *E. coli*	Mudzengi et al. (2017)
Crude aqueous and ethanol extracts of twigs	*C. albicans*, isolates of cariogenic organisms, *S. mutans*, *S. mitis*, and *lactobacilli*, and periodontal pathogens, *Peptostreptococcus*, *P. intermedia*	Ethanolic extract showed a significantly higher activity compared to water extract	Siddeeqh et al. (2016)
Hexane and ethanol extracts	Cariogenic *S. mutans*	A decline in the bacterial cell viability	Halawany et al. (2016)
Methanol extracts of	*S. aureus*, *S. capitis*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*,	The fruit methanolic extract showed highest anti-*Staphylococcus* activity	Noumi et al. (2017)

(continued)

Table 3.4 (continued)

Plant parts/ extracts	Microorganisms used	Results	References
fruit, leaves, and stems	*S. warneri*, *S. xylosus*, *S. saprophyticus*, *C. violaceum*, *P. aeruginosa*	compared to the stem extract and leaf extract and it is more effective than ampicillin	
Chewing stick extract	Clinical isolates of *S. mitis* and *S. sanguinis*, *S. mutans*	Bacteriostatic effect and quite comparable before or after meal	Fatin-Majdina et al. (2014)
Ethanol extracts of leaves and bark	Multidrug-resistant (MDR) strains and clinical isolates of *N. gonorrhoeae*	*S. persica* leaves and bark displayed significant antibacterial activity against *N. gonorrhoeae* strains, including strains resistant to penicillin and ciprofloxacin	Shokeen et al. (2009)
Ethanol and aqueous extracts of bark	Isolates of *A. baumannii*, *C. freundii*, *K. oxytoca*, *P. mirabilis*, *P. vulgaris*, and *P. aeruginosa*	Ethanolic extract being more effective compared to the aqueous extract and *P. aeruginosa* was resistant to both extracts	Rath et al. (2012)
Methanol extract of stem and leaves	*M. violaceum*, *B. megaterium*, *C. fusca*, *P. falciparum*, *L. donovani*, *T.b. rhodesiense*, *T. cruzi*	Both extracts possess mild antimicrobial activity against *M. violaceum* and was ineffective against *B. megaterium* and *C. fusca*. Effective against *P. falciparum* strain but not effective against *T.b. rhodesiense* and *T. cruzi*	Ali et al. (2002)
Methanol extract of bark	Periodontitis isolates of *Staphylococcus*, *Streptococcus*, *Lactobacillus*, *Enterococcus*, *E. coli*	Concentration-dependent inhibitory activity against all tested organisms	Alireza et al. (2014)
Methanol extract of stick	Isolates of *S. aureus*, *S. saprophyticus*, *S. epidermidis*, *S. mutans*, *E. coli*, *Lactobacillus* sp., *C. albicans*, *Candida* sp., *Penicillium* sp.	Dose-dependent inhibitory activity against all tested organisms	Chelli-Chentouf et al. (2012)
Ethanol extract of stem and leaf	*S. aureus*	Stem and leaf extracts were less effective than ampicillin. Combined effect of extracts is highly effective. Combined effect of stem and leaf extracts with two antibiotics was more effective compared to using the extracts only	Ahmed et al. (2010, 2012)

(continued)

Table 3.4 (continued)

Plant parts/ extracts	Microorganisms used	Results	References
Methanol extracts from the bark, leaves, root, and shoots	*C. violaceum*, *E. faecalis*—molecular screening	Anti-quorum sensing ability against *E. faecalis*	Rezaei et al. (2011)
Ethanol extract	*Herpes simplex*	Inhibited the replication	Taha (2008)
Flavonol glycosides constituent	COVID-19	Significant protease inhibitory effect than darunavir, a currently used COVID-19 protease inhibitor	Owais et al. (2020)
Ethanol and hexane extracts of root	*S. mutans*, *S. sanguinis*, *S. salivarius*	Ethanolic extract showed greater inhibition	Balto et al. (2017)
Aqueous extract of miswak root	*St. mitis*, *St. salivarius*, *Strep. mutans*, *S. aureus*, *B. subtilis*, *P. aeruginosa*, *E. coli*, *S. typhimurium*, *C. albicans*	Effective antibacterial activity	Abou-Zaid et al. (2015)
Aqueous extract of root	Oral isolate: *C. albicans*	Promising antifungal activity	Al-Bagieh et al. (1994)

3.6.2 Antiplasmodial and Anthelmintic Activity

The anthelmintic potential of aqueous extracts from the shoots and leaves was evaluated against strongyle nematodes, and its efficacy was compared with albendazole and levamisole (Reuben et al. 2011). In vitro anthelmintic activity of the extracts was shown to be effective in a concentration-dependent manner. Aqueous and alcoholic root extracts of *S. persica* at 10, 20, 40, and 80 mg/mL concentration were compared with piperazine citrate, and the results are promising (Majeed 2011). Ali et al. (2002) investigated 19 plant species that have traditionally been used to treat malaria and other tropical ailments in Sudan. Different extracts of *S. persica* were discovered to have antiplasmodial action against the *P. falciparum* NF54 strain.

3.6.3 Release of Calcium and Chloride into Saliva

The influence of miswak on the composition of mixed saliva converging on ion release was studied in the short and medium term (Gazi et al. 1992). Authors observed that miswak use led to a significant increase in the levels of calcium and chloride ions (22- and sixfold, respectively) along with a significant decrease in pH

and phosphate concentration. The beneficial effects of miswak in dental hygiene could be attributed to their ability to release and increase the levels of calcium and chloride ions in saliva.

3.6.4 Tick-Repellent Properties

A study in 2009 reported that the oils of *S. persica*, *Pistacia*, and *Juniperus phoenicea* possess significant but short-duration tick-repellent effects against host-seeking *Ixodes ricinus* nymphs (Garboui et al. 2009).

3.6.5 Anti-caries and Periodontal Potential

Regular use of *S. persica* plays an important role in dental caries prevention. Aldini and Ardakani (2007) examined the effectiveness of a natural toothbrush to a miswak in the prevention of dental cavities. The study findings revealed that treatment groups were significantly more protected than the control group. Data showed that control group was at the higher risk of developing dental caries (more than ninefold) in comparison to the study group for each tooth. Several studies showed that cleaning mouth by swashing or rinsing with miswak extract instead of water leads to caries prevention. Increase in the pH and plaque level in addition to the stimulation of parotid gland secretion might seem to be the mechanism of caries prevention (Sofrata et al. 2007; Sorna Kumari et al. 2011). *S. persica* extract has an antidental caries effect, particularly at a concentration of 35%, because it inhibits the growth of *E. faecalis* planktonics which is mainly responsible for oral disease (Sari et al. 2016). Stem, root, and bark extracts of *S. persica* are rich in nitrogenous compounds like caffeine, theobromine, and trigonelline. Forty percent stem extract exhibited broad-spectrum efficacy against a panel of bacteria and fungi that cause the majority of tooth cavities, henceforth ratifying the therapeutic potential of the plant (Chabane et al. 2017).

According to Mohammed et al. (2006), miswak, as well as other toothbrushes, reduced plaque coverage in the anterior and posterior regions and found that miswak in both experimental and clinical studies was equally effective as a toothbrush in eliminating plaque on buccal teeth surfaces. Salman et al. (2005) observed that the aqueous extract (10%) of *S. persica* is an effective antibacterial agent. Aqueous extract of *S. persica* was found to be an effective antibacterial irrigant in the endodontic treatment of teeth having necrotic pulps. Khalessi et al. (2004) tested the oral health efficacy of persica mouthwash (which contains a *S. persica* extract) and compared the results with a placebo mouthwash. The study revealed that persica mouthwash not only improved the gingival health but also reduced cariogenic bacterial load. However, persica mouthwash failed to reduce the accumulation of dental plaque. Results of several other studies have demonstrated miswak to be as good as teeth brushing. It showed comparable efficacy in reducing plaque and gingivitis (Al-Otaibi et al. 2003; Poureslami et al. 2007; Hattab 1997). A study

was carried out on 480 adults (aged 35 to 44 years and 65 years and older) in Mecca and Jeddah cities of Saudi Arabia using miswak stick from the root of *S. persica*. Authors found that participants who used the miswak frequently had the healthy oral hygiene. Therefore, they concluded that use of miswak could potentially decrease the need for the oral disease-related treatment. Gingival inflammation and bleeding on probing were reduced by rinsing the mouth with a slurry of miswak toothpaste and displayed strong antiplaque effects (Al-Khateeb et al. 1991; Jassoma et al. 2019). Eid and Selim (1994) found that the use of miswak may influence periodontal health and may be considered for gingival recession.

3.6.6 Anti-inflammatory and Analgesic Potential

Miswak decoction was observed to be more effective against thermal stimuli than chemical stimuli in a mice model (Mansour et al. 1996). *S. persica* decoction exerts a considerable anti-inflammatory effect in rats with carrageenin-induced paw edema (Monforte et al. 2001). Contrary to this, aqueous extract of *S. persica* was noted to exhibit only weak anti-inflammatory activity (Ezmirly et al. 1979). Sulaiman et al. (1996) investigated the analgesic effects of a decoction of miswak roots and branches. Plant decoction decreased the sensitivity of mice to both chemical and thermal stimuli in a concentration-dependent manner. For the hot plate, tail flick, and writhing reflex tests, the effective doses (ED_{50}) were observed to be 3.5, 4.5, and 5.5 mL/kg, respectively. In mice, the ethanolic extract of *S. persica* could elicit a dose-related strong analgesic effect. This activity was significant at 500 and 700 mg/kg body weight (bw) and was at par with the standard drug aspirin (Hoor et al. 2011, 2014). An ethyl acetate extract of *S. persica* leaves at a dose of 500 mg/kg body weight i.p. showed substantial analgesic efficacy in albino mice (Rajesh et al. 2010). The organic extracts of miswak stick, viz., ethanol and ethyl acetate, were found to dramatically reduce edema thickness in experimental animals (Ibrahim et al. 2011a).

3.6.7 Enzyme Inhibitory Activity

S. persica exhibits inhibitory activity against angiotensin-converting enzyme (ACE) and tyrosine kinase (TK). Nyman in 1998 evaluated and compared the ACE inhibitory potential of various aqueous and organic extracts of *S. persica* leaves and unripe seeds. The activity was evaluated at a concentration of 0.33 mg/mL. ACE inhibition was found to be associated with the polarity of the extract. In general, unripe seed extracts showed better inhibition of ACE than the leaves extract (24–55% vs. 14–21%). The most polar aqueous extract exhibited the highest ACE inhibition (55% and 21%, for seed and leaves, respectively), and the lowest inhibition was shown by acetone extract (24% and 14%, respectively). Ethanol extract being more polar than acetone could inhibit 36% and 19% of ACE activity. The findings suggested that seeds contain higher level of phytochemicals capable of acting as ACE inhibitors and thus could be used in the treatment of cardiovascular

diseases (Nyman et al. 1998). On the other hand, Muddathir et al. (2017) found that a methanolic extract of *S. persica* leaf could be a potential source of anticancer compounds. They showed that the leaf extract at a concentration of 500 μg/mL was able to inhibit the tyrosinase kinase enzyme activity.

3.6.8 Antifertility Activity

Antifertility effect of miswak extract investigated in female mice model did not produce significant effect on their fertility, although treatment with miswak did induce a considerable drop in the relative weights of the ovary along with gain in the uterine weights. Male mice exposed to miswak had 72% decrease in pregnancies in untreated females impregnated by test males (Darmani et al. 2003). According to the findings, *S. persica* appears to have negative consequences on the fertility and reproductive organs of both male and female mice. Because of the presence of phytoestrogen components in *S. persica*, its combination with *A. barbadensis* can boost estrogen levels without deleterious effect on the vital organs and thus can be used as safe contraceptive therapy (Helal et al. 2015). It has been reported that the addition of *S. persica* extract in 0.2–0.25% concentration to the rabbit foods increased their productivity and reproductive performance (El-Kholy et al. 2008).

3.6.9 Anticonvulsant and Sedative Activity

S. persica stem extracts have the ability to potentiate sodium pentobarbital (NaPB) and pentylenetetrazol (PTZ) activity on the rats. *S. persica* extracts increased sleeping time and lowered NaPB induction time. It also protected against PTZ-induced convulsions by lengthening the latency period and lowering the fatality rate (Monforte et al. 2002).

3.6.10 Antiulcer Activity

Monforte et al. (2001) investigated the antiulcer potential of a lyophilized decoction prepared from stems and roots of *S. persica* in rodents. Aspirin-induced ulcer in Wistar albino rats showed significant improvement, indicated by a decrease in ulcer index, upon treatment (500 mg/kg, once daily) with the lyophilized stem and root decoctions for 7 days. Furthermore, the decoction of *S. persica* exerted anti-inflammatory effects. Antiulcer activity of *S. persica* twigs is also reported. The results of optical microscopy showed that *S. persica* twigs in a lyophilized decoction form at a dose of 500 mg/kg bw could protect and repair the damaged components of the gastrointestinal mucosa in male Wistar rats. The treatment could not restore the normal texture of the epithelial layer completely, but it brought back the gastric glands and lamina propria almost to the normal distribution (Sanogo et al. 1999).

3.6.11 Hypolipidemic and Hypoglycemic Activity

Treatment of male Wistar rats with the *S. persica* extracts has been shown to decrease the elevated levels of triglycerides and improve HDL levels in male Wistar rats (Khan et al. 2014). Aqueous root extract of Arabian *S. persica* is reported to exhibit hypoglycemic activity in an acute study. For streptozotocin (STZ)-induced hyperglycemia in rats (60 mg/kg), oral administration of aqueous suspension in a dose of 500 mg/kg (3% v/v with Tween 80, once daily) for 2 weeks was able to decrease the elevated blood sugar level (>75%) in blood glucose. The hypoglycemic effect of *S. persica* extract was similar to the effect produced by the positive control glibenclamide. *S. persica* stem decoction has also been reported to possess hypoglycemic properties. It was also found to increase the level of immunoreactive insulin in plasma along with a higher threshold of oral glucose tolerance in experimental studies. In addition, the stem decoction resulted in a considerable reduction in average body weight (Trovato et al. 1998). Another study showed that giving diabetic adult albino rats 70% hydro-alcoholic *S. persica* root extract at two concentrations, 200 and 400 mg/kg bw, effectively lowered blood glucose and lipid profile levels (Hooda et al. 2014). A decoction of *S. persica* could exhibit favorable effects in experimentally induced hypercholesterolemia in rodents and was successful in bringing back the cholesterol and LDL to the normal levels (Galati et al. 1997). In continuation of their interest, Galati et al. (1999) studied the effect of a lyophilized stem decoction of *S. persica* on hypercholesterolemia. They found that the lyophilized preparation at a dose of 500 mg/kg provided significant protection against the recurrence of diet-induced hypercholesterolemia (Galati et al. 1999). Saini and Yadav (2013) evaluated the hypoglycemic efficacy of alcoholic extract of *S. persica* aerial parts at a high dose of 2000 mg/kg bw. The extract was suspended in 1% CMC prior to administration *po*. The extract lowered the blood sugar level not only of diabetic animals but also of normal rats. The hypoglycemic effect of the extract was similar in potency to the antidiabetic drug tolbutamide (Saini and Yadav 2013). Iyer et al. (2012) compared the hypolipidemic capacity of ethanolic and chloroform extracts of *S. persica* stems. It was noted that non-polar extract (chloroform) was better than the polar alcoholic extract at both the tested doses of 200 and 400 mg/kg bw indicating that chloroform extract is rich in phytochemicals that could lower the elevated levels of triglycerides and cholesterol induced by triton in rats (Iyer et al. 2012). Iyer and Patil (2012) isolated a phytosterol, namely, stigmast-5, 22-dien-3 β-ol, from the stems of *S. persica* in order to identify the chemical substance responsible for the bioactivity. The isolated phytosterol following oral administration at a lower dose of 200 mg/kg for 5 days had the capacity to significantly normalize the elevated lipid parameters and enhance the level of HDL in triton-induced hyperlipidemia in rats. It was concluded that the isolated compound is more potent than the chloroform extract (Iyer and Patil 2012).

3.6.12 Locomotor Activity

The beneficial actions of *S. persica* extracts on mice exploratory locomotor activities were studied by Sulaiman et al. (1986). *S. persica*-treated mice's exploratory movement slowed down more quickly than control mice's. Mice treated with *S. persica* extract also experienced much lesser number of stereotypical movements.

3.6.13 Diuretic Activity

S. persica leaves decoction is used traditionally to increase the diuresis. The diuretic potential of its methanolic leaves extract in normal rats was assessed by Bhadoriya and co-workers in 2010. The methanolic extract showed a pronounced diuretic effect in comparison to the positive control drug hydrochlorothiazide (Bhadoriya et al. 2010).

3.6.14 Antipyretic Activity

A randomized, double-blind clinical interventional study found that oral administration of a polyherbal ayurvedic preparation of *S. persica* can decrease fever quickly and significantly (Gupta et al. 2008). In comparison to aspirin, the antipyretic effect was more persistent and significant (Gupta et al. 2008).

3.6.15 Cytotoxic and Anticancer Activity

The cytotoxic effects of miswak and chlorhexidine were studied by Rajabalian et al. (2009). Findings revealed that mouthwash containing miswak and chlorhexidine possesses favorable activity against macrophage, epithelial, fibroblast, and osteoblast cells. In vitro studies of *S. persica* root extracts on human gingival fibroblast cells were conducted by Balto et al. (2014). *S. persica* ethanol and hexane did not produce any cytotoxicity at 0.5 mg/mL dose. However, when the dose was increased to 1 mg/mL, hexane extract showed some cytotoxicity. It showed cell survival rates of 86% in lactic dehydrogenase assays and 88% in crystal violet assays. The ethyl acetate extract of *S. persica* roots (1 mg/mL) was identified as the most cytotoxic extract having showed cell survival rates of 40% and 66%, respectively, in lactate dehydrogenase and crystal violet assays.

Later studies performed using an aqueous extract of *S. persica* toothbrush showed it to be cytotoxic at 5.75 mg/mL but produced considerable cell proliferation at the lower dose after 24 h. Surprisingly, *S. persica* ethanolic extract produced severe cytotoxic effects on human dental pulp stem cells at 5.75–1.43 mg/mL after 24 and 48 h (Tabatabaei et al. 2015). Albabtain et al. (2017) tested cytotoxicity of miswak and other toothbrushes. They found that benzyl isothiocyanate and miswak essential

oil produced cytotoxic effect against gingival fibroblasts while oral keratinocytes were resistant.

The ethanolic fruit extract of *S. persica* against the cancer cell lines, viz., MCF7 (breast), A2780 (ovary), and HT29 (colon), showed IC_{50} values of 17.50, 8.35, and 5.12 μg/mL, respectively (Al Bratty et al. 2020).

Baba Fakruddin et al. (2018) investigated the anti-inflammatory and anti-cancer activity of various parts of *S. persica* L. Among the aqueous and organic extracts (ethanol and acetone) of the *S. persica* plant parts, ethanolic leaf extract produced significant antiproliferative activity against HeLa cell lines. Al-Dabbagh et al. (2018) highlighted the ability of methanolic fraction of *S. persica* in inhibiting the viability of HepG2 cells. It was suggested that compounds isolated from the extract could be developed as potential anti-tumor agent for hepato-cellular carcinoma. Iyer and Patil (2012) provided the evidence of anticancer activity of a pure compound Stigmasta-5,22-dien-3β-ol isolated from the stem of *S. persica*. It was shown to delay the overall growth of tumor in the animal models. Petroleum ether extract of the *S. persica* bark and sticks is rich in fatty acids and lipids. Surprisingly, it showed remarkable antiproliferative activity in comparison to other organic extracts. It was found to inhibit proliferation of breast (MCF-7), colon (HCT-116), hepatic (HepG2), and lung (A549) cell lines. Its activity was found to decrease in the following order: colon carcinoma> lung carcinoma> hepatocellular carcinoma> breast carcinoma. The IC_{50} values against these carcinoma cell lines were found as 10.2, 19.87, 43.6, and 44.3 μg/mL, respectively (Ibrahim et al. 2011b).

3.6.16 Antioxidant Activity

Methanolic root extract of *S. persica* exhibits in vitro radical scavenging activity against DPPH and ABTS radicals. The antioxidant capacity of the extract was more potent and selective for ABTS radical in comparison to the DPPH radical as indicated by their respective IC_{50} values of 1.6 and 4.8 μg/mL, respectively (Mohamed and Khan 2013).

The presence of glycosides, tannins, saponins, proteins, different phenolic compounds, alkaloids, flavonoids, steroids, and vitamin C in the aqueous extract of *S. persica* could be responsible for scavenging DPPH radicals (62.5%) and preventing lipid peroxidation (42.04%) (Mohammed 2014; Al-Dabbagh et al. 2018). Similarly, another study showed that aqueous and ethanol extracts possess high to extremely high antioxidant activities (Ibrahim et al. 2015). Aqueous and ethanolic root extracts also have the ability to scavenge free radicals comparable to gallic acid, a polyphenolic antioxidant compound (Ramadan and Alshamrani 2016).

Persicaline exhibited promising antioxidant potential and was effective in scavenging DPPH, superoxide anion, and nitric oxide radicals, with IC_{50} values of 0.1, 0.08, and 0.09 μM (Farag et al. 2018). A study was conducted to compare the antioxidant activity of *S. persica* extracts of varying polarities. Authors reported that polar aqueous and alcoholic (methanol and ethanol) extracts were more potent in scavenging DPPH free radicals and in FRAP reducing assay in comparison to the

non-polar (acetone and chloroform) extracts. It was suggested that the antioxidant activity of polar extracts could be due to their chemical composition which showed higher levels of phenolic, flavonoid, and proanthocyanidins (Qasim et al. 2016).

Methanolic extract of *S. persica* bark, seed cake, and leaves from the Sudanese states of Gezira was tested and compared for antioxidant activity. Results indicated that *S. persica* grown in thick clay soil and sandy soil (Kordofan) were significantly beneficial in suppressing linoleic acid oxidation and β-carotene bleaching; however their antioxidant activity was weaker than the positive control butylated hydroxyanisole (Mariod et al. 2009). Based on the in vitro antioxidant assays, it could be inferred that *S. persica* whole plant and its various parts contain natural products which are capable of scavenging DPPH, ABTS, superoxide anion, and hydrogen peroxide radicals (Kumari et al. 2017). Another study compared the antioxidant activity of leaves and stems of *S. persica*. Butanol extract of stem demonstrated stronger antioxidant activity than the leaves extract in terms of scavenging of DPPH radicals. The effect of stem extract was almost 18-fold stronger than the leaves extract (IC_{50} = 14 μg/mL and 257 μg/mL, respectively). Surprisingly, both the leaves and stem extracts showed almost similar ferric reducing capacity (IC_{50} = 3660 μg/mL vs. 3290 μg/mL). This disparity in scavenging of DPPH radicals could be attributable to the composition and chemical nature of phenolics and other secondary metabolites, rather than their content, which are easier to extract using butanol (Kholkhal et al. 2010). Similar comparison between root and stem extracts of *S. persica* was made in rat brain homogenate by Hooda and Singh (2012). Findings revealed root extract to be more powerful antioxidant than the stem extract. Root extract scavenged free radicals (DPPH), inhibited lipid peroxidation, and reduced ferric ions at a much lower dose than stem extract. Furthermore, in comparison to alcoholic and aqueous extracts, the hydro-alcoholic extract was the most effective. Arora and Kaushik (2007) showed hydroalcoholic and aqueous extracts of *S. persica* to possess significantly high scavenging ability against DPPH radicals.

3.6.17 Wound Healing Activity

Couple of research studies have highlighted the usefulness of *S. persica* in would healing. Bore and Tatke (2015) prepared a gel by incorporating 5% w/w of methanolic stem extract of *S. persica and evaluated its potential in wound treatment. The gel treatment was found to be quite effective as it shortened the epithelialization period, increased the tensile strength, and hastened the wound healing process* (Bore and Tatke 2015). In rats, topical application of a gel containing a methanolic fraction of *S. persica* to the excision wound resulted in a greater rate of contraction and a shorter period of epithelialization (Tatke et al. 2018).

3.6.18 Anti-protozoan Activity/Anti-Eimerial Activity

Al-Quraishy et al. (2019) looked into the role of *S. persica* leaf extract in preventing *Eimeria papillate*-induced eimeriosis in mice. The optimum dose of *S. persica* leaf extract that successfully eliminated the oocytes in the feces was observed to be 300 mg/kg, and this effect was almost threefold greater in comparison to the control group.

3.6.19 Antidepressant Activity

Ibrahim and Alnuwaysir (2020) reported the antidepressant activity of the miswak in experimental animals. The effects of aqueous extract of *S. persica* at two different doses (5 and 10 mg/kg bw) on the duration of immobility were compared with the standard antidepressant drug imipramine. The extracts reduced the duration of immobility quite significantly.

3.6.20 Anti-osteoporosis Activity

The efficiency and role of *S. persica* toothbrush (miswak) extract in osteoporosis were examined by Fouda and Youssef (2017). They employed ovariectomized (OVX) rat models, i.e., estrogen-deficient rats, to evaluate the beneficial role of extract on osteoporosis. For 16 weeks, OVX rats were administered (*po*) the *S. persica* stick extract at three different doses of 50, 150, and 300 mg/kg. *S. persica* extract was noted to produce the dose-related protective effects in osteoporosis.

3.7 Phytochemistry of *Salvadora persica* Linn. Plant

The different parts of *S. persica*, namely, root, stem, twig, leaf, and fruit, have been phytochemically profiled. *S. persica* leaves have been reported to contain phenolic compounds (flavonoid glycosides, flavone aglycone, tannins), terpenoids, saponins, and steroids. Most of the phytochemicals could be extracted using aqueous extract (Reuben et al. 2011). Different solvent extracts of varying polarity such as hexane, chloroform, ethanol, and water were used to isolate chemical compounds from the *S. persica* twig and stem. Phytochemical investigation of these extracts revealed presence of different classes of secondary plant metabolites including alkaloids, carbohydrates, phenolic compounds (tannins and flavonoids), and saponins (Gupta et al. 2015). The chemical structures of naturally occurring phytoconstituents isolated from *S. persica* L. are presented in Fig. 3.3.

Nitrogen-containing compounds (pyrrolidine, pyrrole, and piperidine derivatives) are present in the sticks of *S. persica* (Galletti et al. 1993). Sodium 1-*O*-benzyl-β-D-glucopyranoside-2-sulfate (salvadoside), 5,5′-dimethoxylariciresinol 4,4′-bis-*O*-β-D-glucopyranoside (salvadoraside), syringin, liriodendrin, and sitosterol 3-*O*-β-D-

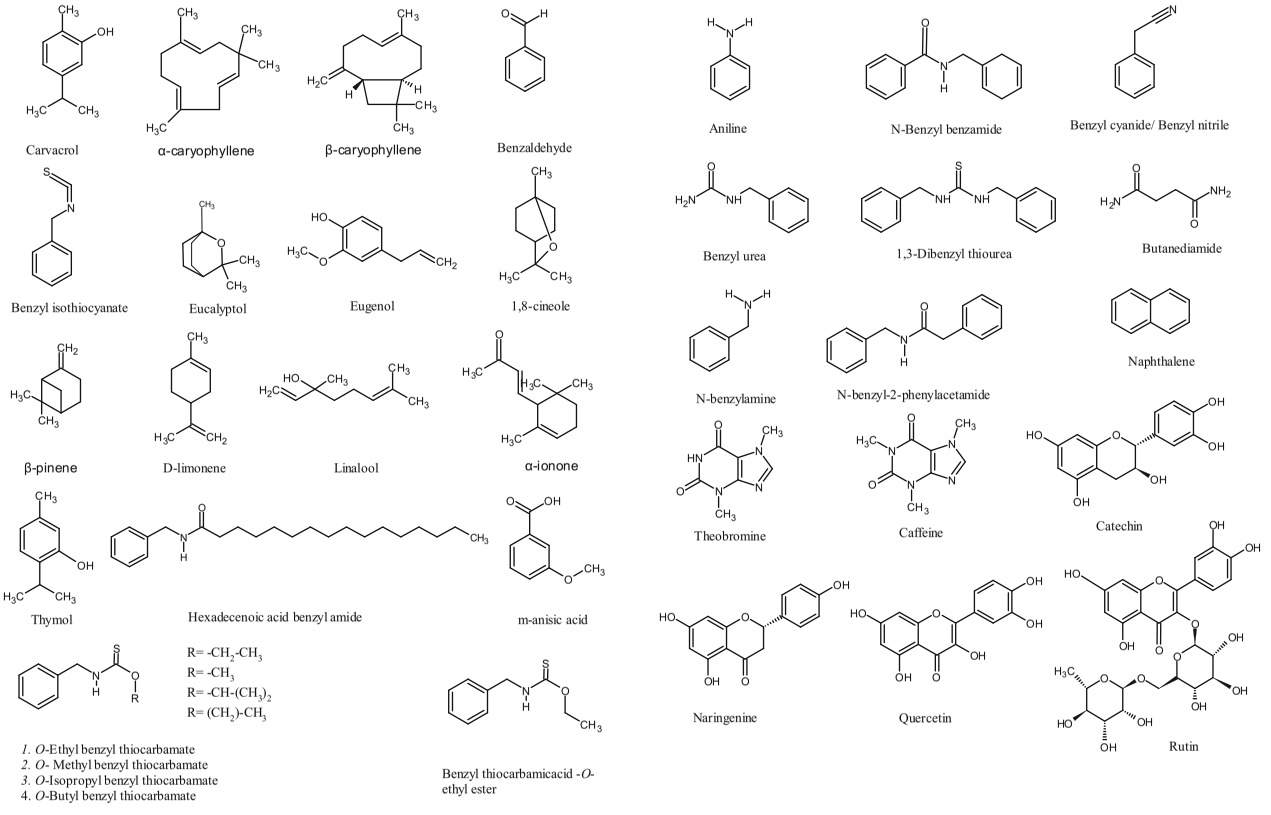

Fig. 3.3 The chemical structures of the major chemical constituents of *S. persica* Linn

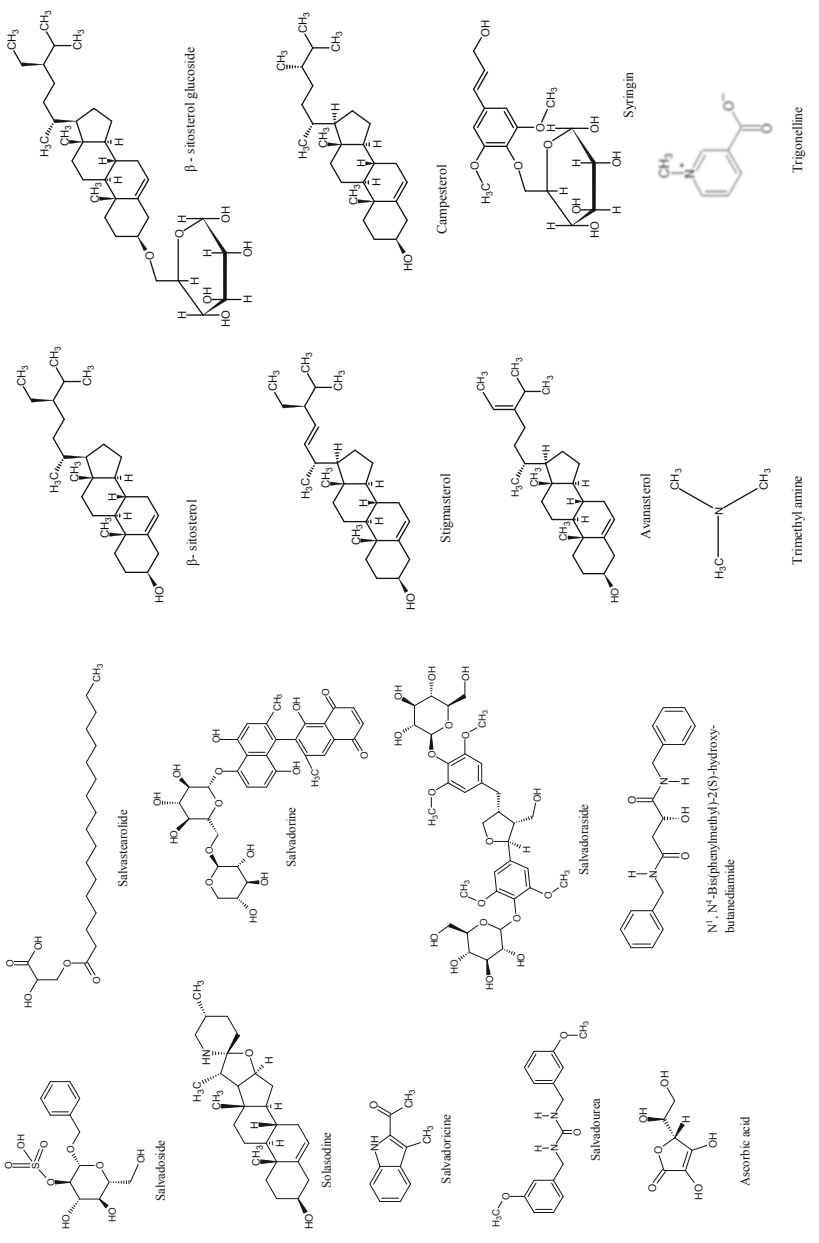

Fig. 3.3 (continued)

glucopyranoside are the five lignin glycosides which were isolated from the stems of *S. persica* (Ohtani et al. 1992).

Khalil (2006) isolated four benzylamides from the stems of *S. persica* which were characterized as butanediamide, N1, N4-bis(phenylmethyl)-2(S)-hydroxy-butanediamide (1), N-benzyl-2-phenylacetamide (2), N-benzylbenzamide (3), and benzylurea (4).

5-*O*-caffeoylquinic acid and 4,5-*O*-D-caffeoylquinic acid were found in the root, whereas 5-*O*-caffeoylquinic acid, 3,5-*O*-D-caffeoylquinic acid, catechin, and epicatechin were found in the stem. The bark of *S. persica* contains 5-*O*-caffeoylquinic acid, naringenin, and a number of alkaloids such as caffeine, theobromine, and trigonelline, according to Chabane et al. (2017).

Benzyl isothiocyanate (52.5%), benzyl nitrile (38.3%), carvacrol (3.3%), benzaldehyde (2.5%), aniline (0.7%), and naphthalene (0.6%) constituents were present in the essential oil extracted from the stems of *S. persica* (Noumi et al. 2011). The major constituent of the volatile oil was 1,8-cineole (eucalyptol) (46%). α-Caryophyllene and 9-epi-(*E*)-caryophyllene together accounted for 19.7%, while β-pinene content was around 6.3% (Al-Ali et al. 2005). The major constituent of *S. persica* leaves essential oil was identified as benzyl nitrile (53.96%). Monoterpenoids were present in significant quantity which could be responsible for the biological activities of leaves. Isothymol, thymol, and eugenol made up around 37% of total constituents. Other identified volatile constituents included isoterpinolene (<0.50%), β-caryophyllene (4.72%), and eucalyptol (0.79%). The presence of these components was confirmed by GC-MS analysis (Al-Ali and Al-Lafi 2003).

The volatile portion of *S. persica* essential oil has also been shown to contain α- and β-thujones, cineole, β-cymene, β-myrcene, camphor, borneol, limonene, linalool, and bornyl acetate, and the non-volatile fraction contained caryophyllene, humulene, β-santalol, and farnesol (Hyson 2003).

Seeds of *S. persica* contain 42% fat which upon hydrolysis gives fatty acids such as lauric acid (47.2%), myristic acid (28.3%), palmitic acid (28.5%), oleic acid (12.1%), and linoleic acid (1.3%), while unsaponifiable seed fat portion contains benzyl isothiocyanate, sitosterol, and s-dibenzyl thiourea (Patel et al. 1926).

Benzaldehyde, β-carbonic acid, 2-cyclohexen-1-one 3-methyl-6-(1-methyl ethenyl), β-damascenone, *E*-2-decanal, dodecanoic acid, β-eudesmol, hedycaryol, 2-hexadecen-1-ol-3-7-11-15-tetramethyl, hexadecanoic acid, heptadecene, α-lonone, indole, linalool, linalyl acetate, 6–10- dimethyl, D-limonene, δ(7) methanone-2, nonadecane, nonanoic acid, octadecanoic acid, 9-octadecanoic acid, 9–12-octadedecenoic acid, 2-pentadecanone-6-10-14-trimethyl, δ-silinene, tricosane, tetradodecanoic acid, 2-undecanone, and 5–9-undecadienz-one 6–10-dimethyl are the additional compounds found in the essential oil of *S. persica* (Abdel Rahman et al. 2003).

The seeds of *S. persica* can be used for cooking. Seeds yield around 40% of edible oil. The major fatty acid is myristic acid (55%) followed by lauric acid, palmitic acid (20% each), and small amount of oleic acid (around 5%). The seeds of *S. persica* also contain fluoride and silica particles (Makwana et al. 1988).

Five different types of glycosides, namely, "sodium 1-*O*-benzyl-β-D-glucopyranoside-2-sulfate, 5,5′-dimethoxyl ariciresinol 4,4′-bis-*O*-β-D-glucopyranoside, syringin, liriodendrin, and sitosterol 3-*O*-glucopyranoside" were isolated from the stems of *S. persica* (Kamel et al. 1992). Seeds bark and leaves are reported to be a source of fatty acid methyl ester (FAME), tocopherols (-α-tocopherol, γ-tocopherol, γ-tocotrienols, and vitamin E,), sterols (phytosterol, sitosterol, β-sisterol, stigmasterol, campestrol, and Δ^5-Avenasterol), and phenolic compounds (Mariod et al. 2009; Awasthi and Mitra 1964). The plant contains sulfur, organic sulfur compounds, ascorbic acid (Cornu and Massot 1975; Daxenbichler et al. 1991; Farooqi and Srivastava 1968; Boulos 1983; Etkin 1981; Kapoor 1990), and small amount of saponin (Von Kampf 1975). Some anionic components like Cl^-, SO_4^{2-}, thiocyanate, and nitrate$^-$ are present in the root and stem of *S. persica* that can be extracted with water (Darout et al. 2000).

The leaves of *S. persica* contain salvadoricine, which is an indole alkaloid and was identified by Malik et al. (1987). The roots and bark of *S. persica* contain an alkaloid salvadorine; upon hydrolytical cleavage, it gives trimethylamine (Farooqi and Srivastava 1968; Ra'ed et al. 1999; Dorland 1988). Two bioactive flavonoids (rutin and quercetin) from the stem of *S. persica* were detected by Abdel-Wahab et al. (1990). Ezmirly and El-Naser (1981) reported presence of salts NaCl and KCl as well as other phytochemicals including salvadourea, salvadorine, saponin, tannins, vitamin C, silica and resin, cyanogenic glycoside, gluco-tropaeolin, and benzyl isothiocyanate in the roots, twigs, and stem extracts of *S. persica*. Salvadourea and β-sitosterol are also found in the underground roots and leaves of *S. persica* (Ray et al. 1975; Malik et al. 1987). Jain and Saxena (1984) isolated octacosanol, 1-triacantanol, β-sitosterol, and β-sitosterol-3-*O*-β-D-glucopyranoside from the stem of *S. persica*. El-Desouky et al. (2017) reported a new acyl glyceride salvastearolide along with other phytosteroids from the seeds of *S. persica*. Plant sterols detected in the seeds were identified as β-sitosterol, stigmasterol, campesterol, Δ^7-campesterol, and Δ^7-avenasterol.

Abdulaal (2018) purified and characterized the cysteine protease enzyme from miswak *S. persica*. Mohamed et al. (2014) purified α-amylase from miswak with the help of column chromatography. Persicaline is an example of a sulfur-containing imidazoline alkaloid derivative that was isolated from *S. persica* roots. Chemically it is 1,3-dibenzyl-4-(1,2,3,4-tetrahydroxy-butyl)-1,3-dihydro-imidazole-2-thione (Farag et al. 2018).

3.8 Patents Granted to *S. persica* Linn

The miswak (*S. persica*) contains natural agents that support the health of teeth and oral mucosa. Some important patents granted to miswak for its application in dental care and other pharmaceuticals are summarized in Table 3.5.

Table 3.5 Patents on *S. persica* Linn. plant

S. no.	Title	Patent no.	Inventors
1.	Bioactivity of methyl palmitate obtained from a mangrove plant *S. persica* L	CA2442576A1	Usha Goswami, Fernandes Nazarine
2.	Bioactivity of methyl palmitate obtained from a mangrove plant *S. persica* L	EP1372679A1	Fernandes Nazarine, Usha Goswami
3.	Bioactivity of methyl palmitate obtained from a mangrove plant *S. persica* L	US patent 6,638,546, 2003	U Goswami, N Fernandes
4.	Biologically active chloroform fraction of an extract obtained from a mangrove plant *S. persica* L	US patent 6,753,021, 2004	Usha Goswami, Nazarine Fernandes
5.	Biologically active chloroform fraction of an extract obtained from a mangrove plant *S. persica* L	EP 1372681 B1 20,070,801	Usha Goswami, Nazarine Fernandes
6.	Biologically active aqueous fraction of an extract obtained from a mangrove plant *S. persica* L	US6428823B1	Usha Goswami, Nazarine Fernandes
7.	Case for tooth cleaning stick	US8973754B2	Ishtiaq Ahmed
8.	Dentifrice	US5009886A	MR Ahmad, OA Barke
9.	Disposable toothbrush	US8533893B2	MS Sayeed
10.	Ergonomic miswak toothbrush with replaceable brush heads	US 2016/0113383 A1	RikeshaVernae George
11.	Meswak toothbrush	WO2016064355A1	Haluk Ateser
12.	Method for extraction and purification of biologically useful molecules from a mangrove plant *S. persica* L	US 2002/0197339 A1	Usha Goswami, Nazarine Fernandes
13.	Method for extraction and purification of biologically useful molecules from a mangrove plant *S. persica* L	US 6,586,021 B2	Usha Goswami, Nazarine Fernandes
14.	Miswak toothbrush	US 2011/ 0302736A1	MS Sayeed
16.	Siwak tooth cleaning instrument	US 8141195B2	Al-Sulaiman FA, Hawwa MA
17.	Use of *S. persica* in oral and dental care for pets	DE10258659B4	Paul Berendsen, Hans-Kervin Bruins, Heinz Prof. Dr. Mehlhorn, Horst Mennemann, Jürgen Dr. Schmidt

3.9 Conclusion

The current review is an up-to-date phytochemical, biochemical, and pharmacological collection of studies performed on *S. persica*. Thorough systematic literature review revealed that *S. persica* is an important medicinal plant with a broad pharmacological spectrum. The different extracts and phytochemicals have been extensively studied for their potential antimicrobial, tick-repellent, enzyme inhibitory, antidiuretic, locomotor, antifertility, anticancer, hypolipidemic, anti-inflammatory, and analgesic activities.

Traditional medicines, which have a long and proven history of treating numerous disorders, have been the focus of research in recent years. The review provides detailed information on the chemical compounds found in various parts of the plant, as well as their biological activity. In this context, more research on *S. persica* is needed in order to uncover hidden areas and practical clinical applications that can benefit humanity.

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Phytochemistry, Pharmacology, and Applications of *Ocimum sanctum* (Tulsi)

4

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Abstract

Ocimum sanctum, an aromatic and medicinal herb, has gained a special importance for its pharmacological potential since time immemorial. The meaning of tulsi in Sanskrit is "Matchless" and called as queen of all the herbs. *O. sanctum* is well known for its religious, spiritual, and cultural sanctity. OS tastes pungent and bitter. Its effect is hot, light, and dry. The root, leaves, and seed of OS possess several medicinal values. Cultivation of tulsi is widely done for its uses in pharmaceutical industry, perfumery, cosmetics industry, and indigenous systems of medicine. Treatment of the several ailments has been successfully performed from the time of Ayurveda. Ayurveda classifies OS as stimulant, aromatic, and antipyretic herbs; it shows activity by alleviating kapha and vata while aggravating pitta. The special attention has been given to essential oils along with herbal extract in scientific research due to their extraordinary potential in pharmacology, aromatic flavors, and extensive traditional practice. These phytochemicals are discovered from a different class of plant secondary metabolites, namely, phenolic compounds, flavonoids, phenylpropanoids, coumarins, tannins, terpenoids, essential oils, fixed oils, and steroids as well as some vitamins and minerals. A plethora of pharmacological activities such as anticancer, antioxidant, anti-inflammatory, anti-stress, free radical scavenger, anti-diabetic, antileishmanicidal, central nervous system (CNS) depressant,

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anticoagulant, ulcer protective, antifungal, hepatoprotective, antihypertensive, cardioprotective, antiasthmatic, immunomodulatory, antifertility, antiulcer, antiviral, and antimicrobial activity have been reported for OS. The different study suggests OS have no toxic effect in humans; peoples are using its leaf and stem from traditional periods of time, so OS is safe for the treatment of diseases directly as herbal medicine or as a nutraceutical for prevention of diseases. The information and data regarding traditional uses, major chemical constituents, pharmacological potentials, clinical study, and marketed formulation of tulsi have been well explored and noted in this chapter.

Keywords

Ocimum sanctum · Medicinal herb · Phytochemistry · Pharmacological potential · Anti-cancer

Abbreviations

3-MeDAB	3′-Methyl-4-dimethylaminoazo- benzene
ABTs	2,2′-Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radical
ADR	Adverse drug reaction
AHH	Aryl hydrocarbon hydroxylase
ALP	Alkaline phosphate
ALT	Aminotransferase
API	Active pharmaceutical ingredients
AQOS	Aqueous extract of *Ocimum sanctum*
AST	Aspartate amino transferase
BCL-2	B-cell lymphoma 2
CAT	Catalase
CCL4	Tetrachloromethane
CD	Cluster of differentiation
CDK4	Cell division protein kinase 4
CK	Creatine kinase
c-Myc	Avian myelocytomatosis virus oncogene cellular homolog
COX	Cyclooxygenase
CYT-c	Cytochrome *c*
DM	Diabetes mellitus
DMBA	7,12-Dimethylbenz (a) anthracene
DPPH	2,2-Diphenyl-1-picrylhydrazyl.
ED_{50}	Effective dose
FBS	Fasting blood sugar level
GAD	Glutamic acid decarboxylase
GGT	Gamma-glutamyl transferase
GK	Glucokinase
GSH	*Glutathione*

GSH-Px	Glutathione peroxidase
GST	Glutathione S-transferases
GSTP1	Glutathione S-transferase pi gene
HbA1C	Hemoglobin A1c
HK	Hexokinase
hTERT	Human telomerase reverse transcriptase.
IL-1β	Interleukin 1 beta
IP	Intra-peritoneal
K_2O	Potassium oxide
LOOH	Lipid hydroperoxide or peroxide
LOX	Lipoxygenase
LPO	Lipid peroxidation
MDA	Malondialdehyde
MFC	Minimum fungicidal concentration
MGMT	Methylguanine-DNA methyltransferase
MIC	Minimum inhibitory concentration
MMP-9	Matrix metallopeptidase 9
MNNG	*N*-Methyl-*N*′-nitro-*N*-nitrosoguanidine
N	Nitrogen
NCCLS	National Committee for Clinical Laboratory Standards
NSAIDs	Non-steroidal anti-inflammatory drugs
ODC	Ornithine decarboxylase
OS	*Ocimum sanctum*
P_2O_5	Phosphorus pentoxide
pAKT	Phosphorylated-serine473-AKT
PARP	Poly (ADP-ribose) polymerase
PC	Pyruvate carboxylase
PCNA	Proliferating cell nuclear antigen
PERK	PKR-like endoplasmic reticulum kinase
PFK	Phosphofructokinase
PGE	Prostaglandin
PP2BS	Post-prandial blood sugar
pRb	Retinoblastoma protein
RDA	Recommended dietary allowance
ROS	Reduced oxide species
SDH	Succinate dehydrogenase
SOD	Superoxide dismutase
T2DM	Type 2 diabetes mellitus
TBARs	Thiobarbituric acid reactive substances
u-EGF	Epidermal growth factor family gene
USDA	United States Department of Agriculture
UTI	Urinary tract infection
UV	Ultraviolets
WHO	World Health Organization

4.1 Introduction

Having an extensive use from prehistoric time, aromatic and medicinal plants have gained attention of researchers and scientists to cure aliments. Edible plants are accepted as a potent biochemists and major sources of phytomedicine since time immemorial (Ross and Kasum 2002; Narendhirakannan and Hannah 2013). Aromatic plants with medicinal potential are increasingly used in several aromatherapy, medicinal market, perfumery, food applications, and cosmetics (Awuchi 2019). The API of most of the drugs discovered these days are found to be isolated from plant source (Mehndiratta et al. 2011). The special attention has been given to essential oils along with herbal extract in scientific research due to their extraordinary potential in pharmacology, aromatic flavors, and extensive traditional practice. A survey of WHO revealed that more than 80% patients in India, Burma, and Bangladesh are treated by traditional system of medicine using crude drug. The holy basil "tulsi" is well known for its religious and spiritual holiness. It is regarded as queen of herbs and comes under the family Labiatae (Raseetha Vani et al. 2009; Naibaho et al. 2013). The Sanskrit meaning of tulsi is "Matchless" and is very specially treated in Hindu culture (Kayastha 2014). A great importance is given to tulsi in the traditional system of medicine such as Ayurveda, Unani, and Siddha (Vogel 1997; Khurana et al. 2016). The phytochemical potential of tulsi is also mentioned in Greek and Romanian system of medicine. It is believed to have originated in India although the geographical distribution of holy basil is tropical Asia, northern and eastern part of Africa, Taiwan, Hainan Island, and certain parts of China. *Ocimum sanctum* is a plant with multiple health benefits. Tulsi is one of the most important sources of medicine. The essential oil and secondary metabolite constituents of tulsi impart extensive pharmacological potential and are suggested to be used for treatment of diarrhea, malaria, ulcer, dysentery, skin diseases, bronchitis, bronchial asthma, eye infections, chronic fever (Prakash and Gupta 2005; Kousik and Baldev 2012; Harun-Al-Rashid et al. 2013), etc. In addition *Ocimum sanctum* also exhibits anticancer, anti-diabetic, antimicrobial, antifungal, adaptogenic, and diaphoretic properties (Kousik and Baldev 2012; Harun-Al-Rashid et al. 2013). This book chapter aimed to collect and compile detail data regarding traditional uses, major chemical constituents, pharmacological potentials, clinical study, and marketed formulation of tulsi.

4.1.1 Morphology

Ocimum sanctum is an erect, perennial herb with characteristic aroma and growing up to height of 30–60 cm (Fig. 4.1). It is commonly propagated through seeds (Pandey et al. 2014). The leaves of tulsi are up to 5 cm long and simple, branched, opposite, obtuse, elliptical, oblong with dentate margin. The small hairy structures are found from the root to stem (Pattanayak et al. 2010). The flowers are small and reddish purple in color presented in compact clusters on cylindrical spikes. Fruits are

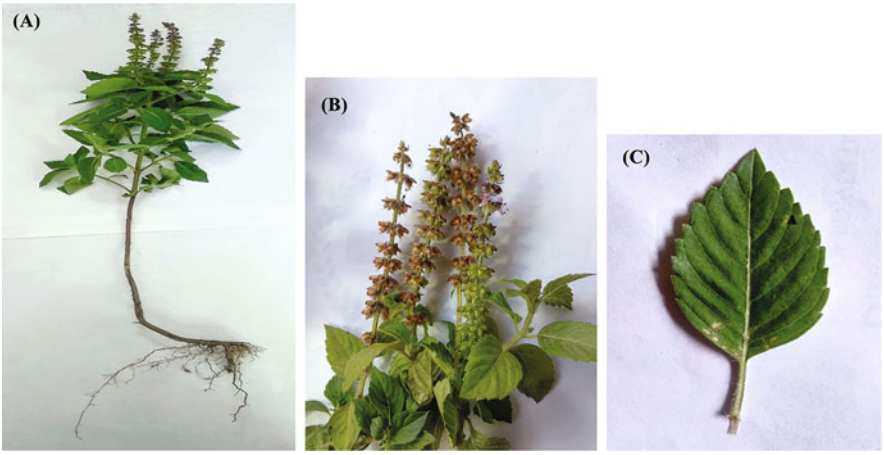

Fig. 4.1 (**a**) Tulsi plant, (**b**) flowers of tulsi, (**c**) tulsi leaf

small and when ripe seeds appear reddish yellow in color. Leaves are light green to dark purple greenish in color (Singh et al. 1996).

4.1.2 Taxonomic Classification

Kingdom: Plantae
Sub-kingdom: Tracheobionta
Super-division: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Sub-class: Asteridae
Order: Lamiales
Family: Lamiaceae
Genus: *Ocimum*
Species: *sanctum*
Binomial name: *Ocimum sanctum* L

4.1.3 Cultivation

Ocimum sanctum is a vital aromatic and medicinal plant which yields several aroma chemicals. Tulsi have wide uses in pharmaceutical industry, perfumery, cosmetics industry, and indigenous systems of medicine. Cultivation of the tulsi pant needs a favorable environment and necessary soil condition to rise into aroma-rich plant (Varghese et al. 2014). The cultivation of *Ocimum sanctum* can be well explained through below mentioned sub-heading (Vidhani et al. 2016; Saran et al. 2017):

(a) **Soil Condition**
Though *Ocimum sanctum* thrives well on a wide range of soils, it is well cultivated in saline and alkaline to moderate acidic soils with rich loam and poor laterite. For better vegetative growth of plant, well-drained soils are preferred (Böhme and Pinker 2014).

(b) **Climate**
The better plant growth with high oil content has been found in high temperature and long days. Tulsi flourishes well under light rainfall and slightly humid conditions. *Ocimum sanctum* is moderately tolerant to frost and drought (Cohen 2014).

(c) **Propagation**
Tulsi is propagated through fresh seeds. There is chance of deterioration due to high cross-pollination, and over generations of seeds, fresh seeds from pedigree stock are selected for plantings (Pattnaik and Chand 1996; Mandal et al. 2000).

(d) **Land Preparation**
The land proposed for cultivation of tulsi is well plowed and brought to fine tilth plot of convenient sizes. The recommended fertilizers of 15 t/ha as basal dose and enough farm yard manure are mixed well in soil (Selvam et al. 2013; Smitha and Tripathy 2016).

(e) **Nursery**
After the well preparation of land for cultivation, elevated seed beds (15 × 4 × 9 ft. size) are thoroughly prepared. 10 kg/bed farm yard manure and 200–300 g seeds/hectare are sown for healthy seedlings (Adhikari et al. 2014; Mridha and Rahman 2015). After sowing of seeds, the seed beds are irrigated using sprinkler hose. The seeds develop buds in 8–12 days, but the seedlings are ready to transfer in another place after 6 weeks at 4–5 leaf stage. After 15–16 days, 2% urea is sprayed before transplantation which promotes the healthy seedling growth (Anbarasan et al. 2016).

(f) **Transplanting**
Transplantation of seedling is done at 4–5 leaf stage with enough spacing for proper respiration of plants (Anbarasan et al. 2016). To get batter and high herbage with quality yield, the seedlings are transplanted at a spacing of 40 × 40 cm or 50 × 30 cm or 40 × 50 cm. Irrigation is done immediately after transplantation (Smitha et al. 2019). The gap filling and replacement of poor basils are done before the second irrigation to get uniform basil stand (Chandelia and Sharma 2011).

(g) **Manure and Fertilizer Application**
It is necessary to frequently restore the soil level to previous condition to get high oil yield. It is necessary to apply farm yard manure at 10 t/ha before planting. Freshly prepared manure and compost prepared from human excreta and city waste are avoided (Singhal et al. 2011). The best fertilizer dose recommended for tulsi cultivation is 120 kg nitrogen (N) and 60 kg P_2O_5 and K_2O per hectare, whereas 120 kg of nitrogen (N) and 105 kg each of P_2O_5 and K_2O per hectare are required for saline and alkaline soils. 50 and 100 ppm

concentration of cobalt and manganese is used as micronutrients (Vetal et al. 2013; Khan et al. 2014).

(h) **Irrigation**
The season and moisture content of soil determine the requirements of irrigation of tulsi (Tomar and Minhas 2004). One irrigation is done immediately after transplantation, and three irrigations per month are done during summer season, whereas irrigation is done as per necessity (Suthar and Saran 2020).

(i) **Weeding**
For proper growth of the plant, weeding is much more necessary. Weeds have to be removed to inhibit the competition with transplanted herb for nutrients. The first and second weeding is done after 1 month and 2 months after planting the herb. Hoeing and earthing up operation is done after the second weeding, and mulch should be used to inhibit the growth of weeds and to maintain soil moisture (Cohen 2014).

(j) **Pest Control**
Few pests and diseases affect tulsi. Thus insecticides and pesticides are used to get rid of such pests. 10,000 ppm concentration of Azadirachtin spray is used to control *Cochlochila bullita* and leaf rollers (Kamaraj et al. 2008; Shetty et al. 2008). Spraying wettable sulfur (4 g/L of water) and drenching Bavistin 1% prevent crops from *Oidium* spp.-, *Rhizoctonia solani*-, and *Rhizoctonia bataticola*-like diseases (Kamaraj et al. 2008).

(k) **Harvesting**
Harvesting of tulsi plant is done after 90–95 days of planting. The crop harvesting is recommended on bright sunny days at full bloom phase to achieve higher amount of essential oil. Tulsi is not supposed to be harvested while there was rain in the previous day (Zheljazkov et al. 2008b). To avoid contamination the herb should be cut at 15–20 cm above ground level, and the surfaces that touch with plant during and after harvest should be cleaned well. The next harvest is done at every 65–75-day interval (Zheljazkov et al. 2008a).

(l) **Expected Yield**
The expected yield of tulsi plant is found to be 5 tons per hectare after harvesting 2–3 times in a year. The whole plant contains about 0.1–0.23% of essential oil with yield of 10–23 kg per hectare (Zheljazkov et al. 2008a).

4.2 Phytochemistry of Tulsi

4.2.1 Chemical Constituents

Several medicinal uses of *Ocimum sanctum* have been discussed along a long year of human civilization. The wide variety of treatments using *Ocimum sanctum* was possible due to its complex chemical constituents. The leaves, stem, roots, inflorescence, and seeds of *Ocimum sanctum* were analyzed. Most components were found in all the plant parts but were in different concentrations. Several phytochemicals like tannins, saponins, phlobatannins, flavonoids, phenolics, terpenoids, glycosides,

Table 4.1 Summary of different phytochemicals present in *Ocimum sanctum*

S. no.	Chemical class	Phytochemical	References
1	Phenolic compound	Caffeic acid (1), chlorogenic acid (2), vanillic acid (3), ocimumnaphthanoic acid (4), methylsalicylic glucoside (5), gallic acid methyl ester (6), gallic acid ethyl ester (7), protocatechuic acid (8), 4-hydroxybenzoic acid (9), vanillin (10), 4-hydroxybenzaldehyde (11), rosmarinic acid (12), caffeic acid ester (13)	Kelm et al. (2000), Aqil et al. (2006), Prasannabalaji et al. (2012), Kaur (2014) and Narendra Babu et al. (2018)
2	Flavanoids	Isothymunin (14), isothymusin (15), cirsimaritin (16), orientin (17), isoorientin (18), isovitexin (19), vicenin (20), apigenin (21), salvigenin (22), crisilineol (23), eupatorin (24), gardenin (25)	Ali and Dixit (2012) and Baliga et al. (2013)
3	Phenyl propanoids	Eugenol (26), eugenyl-β-D-glucoside (27), citrusin C (28), ferulaldehyde (29), bieugenol (30), dehydrodieugenol (31)	Suanarunsawat et al. (2010) and Sonar et al. (2017)
4	Neolignans	Tulsinol A (32), tulsinol B (33), tulsinol C (34), tulsinol D (35), tulsinol E (36), tulsinol F (37), tulsinol G (38)	Varshney et al. (2020)
5	Coumarins	Ocimarin (39), aesculetin (40), aesculin (41)	Pandey and Madhuri (2010)
6	Steroids	B-β, β-sitosterol-3-o-β-D-glucopyranoside (42), stigmasterol (43), campesterol (44)	Kumar et al. (2010) and Pandey and Madhuri (2010)
7	Terpenes	Bornyl acetate (45), β-elemene (46), neral (47), α-pinene (48), β-pinene (49), camphene (50), ocimene (51), β-caryophyllene (52), bergamotene (53), germacrene (54), α-bisabolene (55), β-bisabolene (56)	Muthuraman et al. (2008) and Ahmad et al. (2010)

and steroids with other mineral and micronutrients were confirmed by different chemical tests of various solvent extracts (Singh and Chaudhuri 2018). The phytochemicals present in *O. sanctum* are enlisted in Table 4.1 and Fig. 4.2. Phenolic compounds are important secondary plant metabolites and show notable health benefits. These compounds play different physiological roles in plants; they are used as growth regulators and as important precursor molecules for the biosynthesis of other molecules such as lignin and suberin, which are produced as a defense

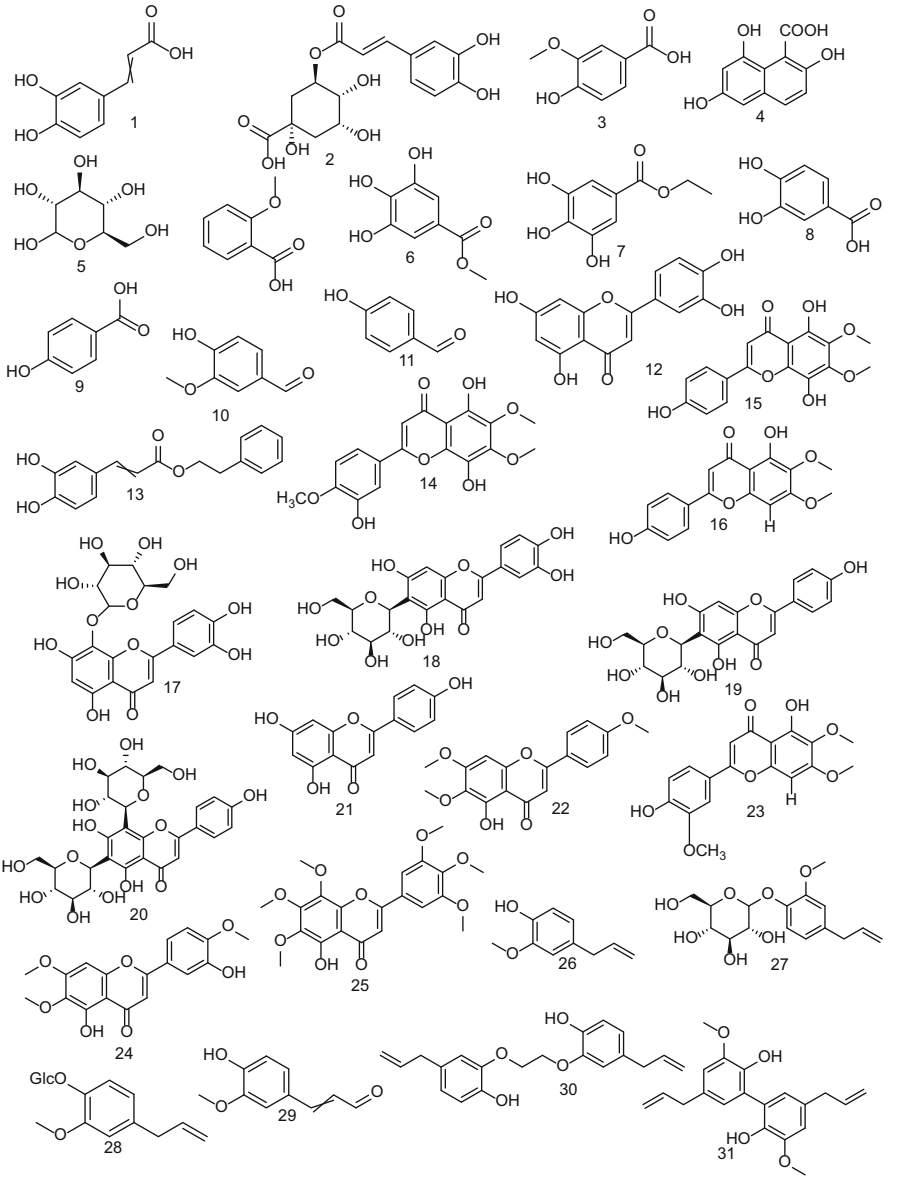

Fig. 4.2 The phytochemicals present in *O. sanctum*

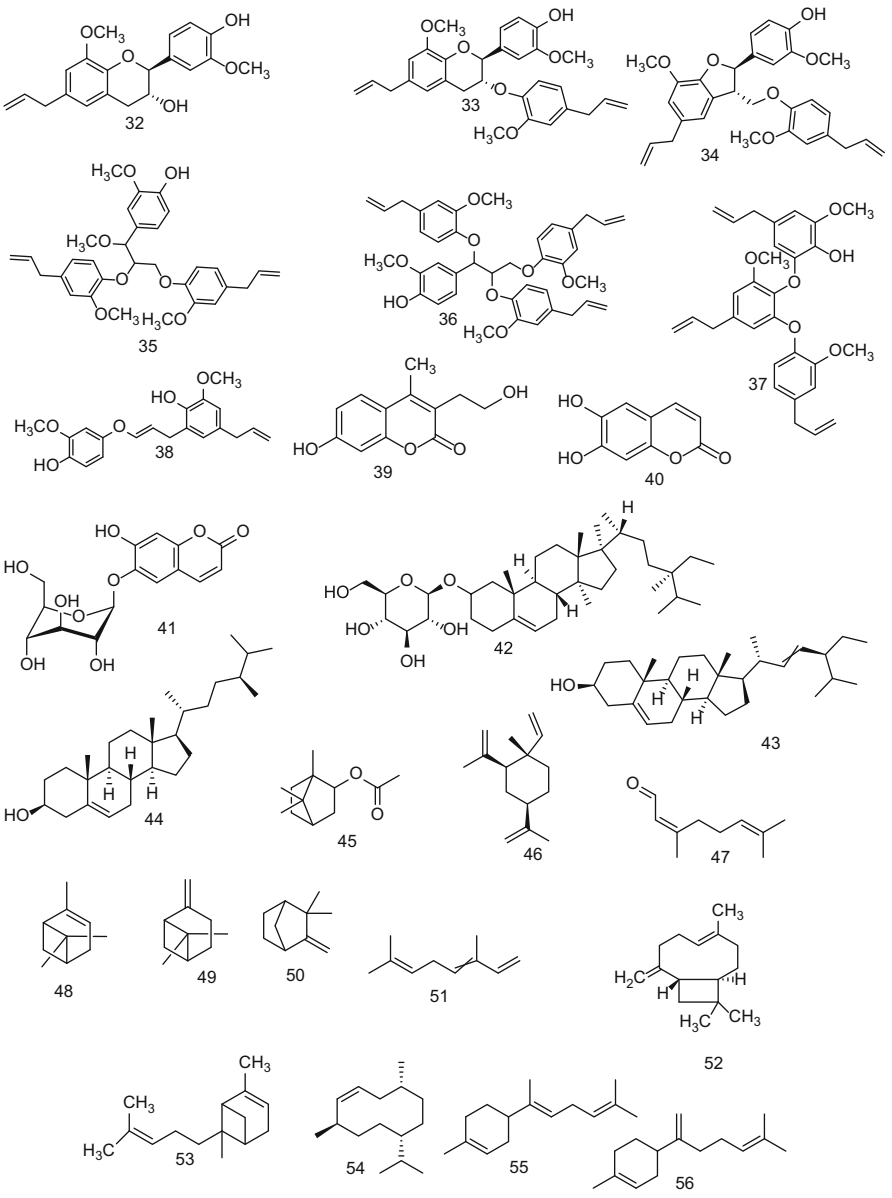

Fig. 4.2 (continued)

against different biotic and abiotic stresses. Terpenes are major constituents of essential oil (Gupta et al. 2007; Mahajan et al. 2013). They are well known for organoleptic properties in various plants. They show many ecological roles, which

include antimicrobial and allelopathic properties along with herbivorous preventive and pollinator attractant.

4.2.2 Essential Oil

Essential oils are secondary metabolites from plants and composed of mainly volatile terpenes and hydrocarbons. They have characteristic strong odor. The quality, quantity, and composition of essential oil in individual plant may vary due to the weather, soil contents, plant organ, age, and vegetative cycle stage (Pandey et al. 2014). *O. sanctum* produces a higher amount of essential oil. The volatile oil from leaves consists of eugenol ($C_{10}H_{12}O_2$) and methyl eugenol ($C_{11}H_{14}O_2$) as major contents and other constituents, namely, carvacrol ($C_{10}H_{14}O$), ursolic acid ($C_{30}H_{48}O_3$), linalool ($C_{10}H_{18}O$), and limatrol (Table 4.2). The volatile oil from seed contains sitosterol ($C_{29}H_{50}O$) and fatty acids (Garg 2005; Salles Trevisan et al. 2006; Nerio et al. 2010).

Besides the secondary metabolites, the study revealed the presence of vitamin C, calcium, and phosphorous along with other micronutrients.

4.3 Ethnobotanical/Traditional Uses

Ocimum sanctum known as tulsi belongs to the Laminaceae family, the and plant is very important because of their healing potentials. OS is medicinally important herb, and it was well known for its medicinal activity from ancient periods of time. OS has been well described for its therapeutics and medicinal activity in Ayurveda and explained as Dashemani Shwasaharni (anti-asthmatic) and anti-kaphic drug (Kaphaghna). In Hindu culture *Ocimum sanctum L.* is sacred, and our ancestors used medicinal plants in daily life in south Asia to treat various illnesses (Gupta et al. 2014). Tulsi is well known as "The incomparable One," "Mother Medicine of the nature," and "The Queen of the Herbs" and is respected as "elixir of life." As tulsi is found to be rich in aromatic nervine essential oils, it is a great choice to sooth the nervous system and support our body's ability to respond the stress. Different parts

Table 4.2 List of bio-active essential oil present in *O. sanctum*

S. no.	Compounds	References
1	Eugenol ($C_{10}H_{12}O_2$)	Pandey et al. (2014) and Salles Trevisan et al. (2006)
2	Methyl eugenol ($C_{11}H_{14}O_2$)	Pandey et al. (2014) and Salles Trevisan et al. (2006)
3	Carvacrol ($C_{10}H_{14}O$)	Pandey et al. (2014) and Garg (2005)
4	Ursolic acid ($C_{30}H_{48}O_3$)	Pandey et al. (2014) and Nerio et al. (2010)
5	Linalool ($C_{10}H_{18}O$)	Pandey et al. (2014) and Nerio et al. (2010)
6	Limatrol	Pandey et al. (2014) and Salles Trevisan et al. (2006)
7	Sitosterol ($C_{29}H_{50}O$)	Pandey et al. (2014), Garg (2005) and Nerio et al. (2010)

Table 4.3 Illustrating ethnobotanical use of tulsi

S. no.	Preparations/parts used	Traditional use
1	Aqueous decoction of tulsi leaves	Treatment of gastric and hepatic disorder
2	Herbal preparation with tulsi whole plant	Symptomatic treatment of viral hepatitis
3	Mixed juice of tulsi with triphala	Use as eye drop for glaucoma, cataract, chronic conjunctivitis
4	Juice of leaves of tulsi	Treatment of chronic fever, dysentery, hemorrhage, and dyspepsia
5	Decoction of tulsi leaves	Remedy for cold
6	Tulsi leaves (crude)	To treat vomiting and used as anthelmintic and antidote for dog bite, scorpion bite, and insect bite
7	Fresh tulsi leaves with pepper	Use as a prophylactic against malaria in the morning time
8	Ayuverdic preparation containing *Ocimum sanctum* L., *Allium sativum*, *Piper nigrum*, and *Curcuma longa*	Antimalarial against *Plasmodium falciparum* and *Plasmodium vivax*
9	Decoction of root of tulsi	Use as a diaphoretic in malarial fever
10	Aqueous decoction of whole plant	Use as anti-diabetic to lower the blood sugar level
11	Paste of tulsi leaves	Treatment of ring worm and other skin diseases
12	Fresh leaves and flower tops of *Ocimum sanctum*	Used as smooth muscle relaxant
13	Seed of tulsi (crude)	Treatment of disorder of genitourinary system

like leaves, flowers, stem, root, seeds, etc. of tulsi plant have been used by traditional experts as expectorants, pain reliever, antiasthmatic, antiemetic, diaphoretic, anti-diabetic, hypotensive, antistress, anticold, stomachic etc. (Pandey and Madhuri 2010). The contemporary preparations of this sacred plant are herbal tea, decoction of leaves, powder in dry form, and preparation of fresh leaves with honey or ghee. The traditional or ethnobotanical use of tulsi (Table 4.3) can be well summarized in points (Mallikarjuna et al. 2011; Bhattacharyya and Bishayee 2013; Kumar et al. 2013; Gupta et al. 2014):

- It is applied on affected surface to reduce swelling and pain.
- Tulsi is effective in various skin disorders. Traditionally people use its paste to treat rashes, insects' bites, and itching. Tree or whole plant is used in ring worm infections and also leukoderma (Gupta et al. 2014).
- Freshly prepared juice of *OS* is applied in nasya karma to get relief from headache and disease of the head and neck.
- Leaf extract is used for cosmetic purpose to reduce scars, acne, and pimples.
- It is used to treat indigestion, constipation, and intestinal parasite.
- Dry and crush leaves of tulsi are very efficient to cure fever and lower respiratory tract problems.

- Traditionally it is efficiently employed as cardiac tonic and blood purifier.
- It has been used as mild aphrodisiac to treat impulsive ejaculation.
- People use it as anti-diabetic, hepatoprotective, and hypolipidemic agent from very ancient time.
- Fresh juice obtained after crushing the leaves of tulsi is widely used for myringitis (inflammation in internal ear).
- The leaves of *Ocimum sanctum* have been widely used to stop bleeding, cure eye diseases, and heal wounds in ruminants.

4.4 Pharmacological Potential

Several scientific studies have discovered plethora of pharmacological potential of tulsi extract (steam distilled, pet. Ether extract, benzene extract) on the various systems like cardiovascular system, immune system, CNS, gastric system, and urinary system (Joshi et al. 2013). Exploring the literatures and scientific researches, it is found that tulsi shows a unique pharmacological activity that promotes health and resilience. Tulsi was used as potent adaptogens from ancient time in India which helps to relieve from the stress and the promotion of homeostasis (Cohen 2014). After much more study, it is shown that tulsi undeniably possess many pharmacological potentials. Various study shows that OS has a unique combination of actions that include antimicrobial, mosquito repellent, anti-diarrhea, antioxidant, anti-cataract, chemoprevention, radioprotection, hepatoprotection, neuroprotection, cardioprotection, anti-diabetic, anti-hypercholesterolemia, anti-hypertensive, anti-carcinogenic, analgesic, anti-pyretic, anti-inflammatory, anti-allergic, immunomodulatory, central nervous system stress, memory enhancement, anti-asthmatic, anti-tussive, diaphoretic, anti-thyroid, antifertility, antiulcer, anti-emetic, anti-spasmodic, antiarthritic, anti-stress, anti-leukodermal, and anti-coagulant activities (Buddhadev et al. 2014; Chandra and Abad Farooq 2014; Hussain et al. 2017).

4.4.1 Stress Resilience

Ocimum sanctum has been documented for extensive stress resilience in modern medicinal and pharmacognostic researches and studies. It has been found that tulsi possesses a potent adaptogenic properties (Mahdi et al. 2003). Preclinical studies have shown that *Ocimum sanctum* avoids stress-induced ulcer in rats in comparison to antidepressant drugs. It was found that tulsi plant extract exhibits anti-stress activity in albino rats by improving SDH level (Singh et al. 2012c). The abovementioned pharmacological potentials help the mind to cope up with several variety of chemical, physical, infectious, and emotional stress to reestablish psychological as well as physiological functions. Chewing 12 leaves of tulsi twice a day helps a person to get efficient relief from stress (Jothie Richard et al. 2016).

4.4.2 Anti-diabetic Potential

Diabetes is a metabolic disorder where level of sugar is increased in blood either because pancreatic β-cells are unable to produce sufficient insulin or because the body system is unable to respond to the insulin produced by the body. Tulsi is reported as anti-diabetic in many researches and studies. It is found to be much more effective in diabetes mellitus. Consumption of aqueous decoction of whole plant lowers the blood sugar level (Patil et al. 2011a). The ethanolic extract of the *OS* is subjected to the perfused pancreases for insulin secretion. It is observed that ethanolic extract stimulates the physiological pathway of insulin secretions by assessing the three important enzymes, i.e., glucokinase (GK), hexokinase (HK), and phosphofructokinase (PFK), along with insulin-dependent and insulin-independent tissues from the brain and kidney (Rani and Khullar 2004). Similar study has been conducted and was found reports eliciting a significant drop in mean FBS level from 174.35 mg/dL to 114.50 mg/dL, PP2 BS from 247.31 mg/dL to 152.02 mg/dL, and HBA1C. Furthermore preclinical studies have reported that use of both aqueous and alcoholic extracts of *OS* showed significant decrease in the level of blood sugar and glycosylated hemoglobin. The anti-diabetic properties of tulsi reported by various studies concluded that treatment of AQOS (aqueous extracts of *Ocimum sanctum* L.) significantly lowered blood glucose level in DM rats; this concludes the fall in fasting blood sugar and HbA1C (Patil et al. 2011b; Grover et al. 2002).

4.4.3 Antifungal Activities

Mycosis is the common fungal infection caused by the inhalation of spores of fungi or contact of fungal colony with skin. Keeping the body clean and staying in the dry environmental condition will minimize the infection though there is need of fungicides (Pandey and Madhuri 2010). The spectroscopic analysis of *Ocimum sanctum* revealed the presence of higher composition of methyl chavicol and linalool which have good antifungal activity against *Candida* and can be applied in treatment of various fungal infections (Singh and Chaudhuri 2018). The synergetic effect of essential oil of tulsi extract with azole (ketoconazole and fluconazole) is reported for candiodosis. The combination of ethanolic extract of leaves of tulsi with *Cassia alata* has shown anti-Cryptococcus activity even at higher temperature and lower pH. The investigation of antifungal activity of tulsi against dermatopathic fungi by 38A NCCLS method showed 200 μg/mL as MIC (minimum inhibitory concentration) and MFC (minimum fungicidal concentration) (Garg 2005). Extract of *Ocimum sanctum* disturbs ergosterol biosynthesis and membrane integrity and acts as antifungal medicine (Balakumar et al. 2011).

4.4.4 Antihypertensive and Cardioprotective Activities

Cardioprotective activities of *Ocimum sanctum* are found greatly effective in myocardial necrosis induced by isoproterenol in Wistar rat through upgrade of endogenous antioxidants (Singh et al. 2012b). Protection against the adriamycin (ADR)-induced lipid peroxidation in heart and liver microsomes is achieved by the ursolic acid derived from *Ocimum sanctum* (Zehra et al. 2019). The OS has been noted for the significant forestallation of transient cerebral ischemia and long haul cerebral hypoperfusion. Basic unsaturated fat contents like linoleic and linoleic acids promote the production of PGE 1 and PGE 3 which restrain the arrangement of PGE 2. Thus *Ocimum sanctum* offers huge assurance against the treatment of hypertension and cardiac problems (Krishna et al. 2014).

4.4.5 Hepatoprotective Activity

Ocimum sanctum shows response to the hepatoprotective activity. The studies have revealed that OS progresses the metabolic breakdown, purging dangerous/toxic chemicals from blood promoting healthy liver work (Singh et al. 2012a). Aqueous extract of tulsi shows the synergistic effect with gentamycin to control the rise in serum creatinine and urea in blood (Pandey and Madhuri 2010). The hepatoprotective potential of tulsi is also noted for the hepatotoxicity by paracetamol in rat. Hydro-alcoholic extract of tulsi leaves on oral administration (200 mg/kg) shows remarkable protection against liver injury induced by paracetamol. It was achieved by significant drop of serum enzyme aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) (Cohen 2014). Marked reduction in fatty acid degeneration of liver was also seen in histopathological examination. Leaves and seeds of tulsi have been detailed for diuretic activity and diminishment of urinary uric acid in albino rabbits. The continuous administration of water extract (3 g/100 g) of tulsi leaves for 6 days orally was beneficial against CCL4-induced liver dysfunction in albino rats (Lahon and Das 2011).

4.4.6 Antioxidant Activity

The physiological process like generation of energy in mitochondria, cell development regulation, and detoxification of xenobiotic in the human body leads to the formation of reactive free radicals (Kelm et al. 2000). The stressful lifestyle and various environmental factors like pesticides, chemical pollutants, and UV radiations contribute to ROS overproduction which causes tissue damage leading to deterioration of health condition. The phytoconstituents and secondary metabolites have significant role in scavenging the free radicals. Antioxidants from the tulsi, especially polyphenolic compounds, effectively impede hydrolytic and oxidative enzyme, decrease blood glucose and lipid level, and enhance immunity; therefore

flavonoids have attracted attention to different issues mainly oxidative stress (Aqil et al. 2006). Existence of hydroxyl groups and keto group in phytochemicals of OS imparts free radical scavenging property and produce antioxidant activity (Shetty et al. 2008). Various in vitro study and research have been done to access the antioxidant potential of tulsi extract. Remarkable results were obtained in scavenging DPPH radical, superoxide radicals, ABTS radical, hydroxyl radicals, and reduction of phosphomolybdate ion (Veeru et al. 2009).

4.4.7 Antifertility Activity

Ocimum sanctum has significant antifertility activity in animals. It has been noticed from phytoconstituents from leaves, ursolic acid. The impact has been attributed to its antiestrogenic impact in male and inhibitory impact on ovum implantation in females. The OS leaves extract on benzene and petroleum ether showed 60–80% of antifertility activity in female rat. The extract of *Ocimum sanctum* in male rats exhibited increase sperm count, motility, and also weight of testis (Pandey and Madhuri 2010; Pattanayak et al. 2010).

4.4.8 Antiarthritic Activity

The antiarthritic potential was assessed against various chemicals produced from joint inflammations in rodents. Due to mimicking human rheumatoid diseases, Freund's complete adjuvant-induced arthritis in the rat is an extensively used model to perform preclinical studies. For evaluation of antiarthritic potential, rat was injected with adjuvants, and inflammation in paws and joint nodules within the ear and tail (delayed systemic response) was induced. For the management of induced arthritic disease, fixed oil of OS was given at dose of 3 mL/kg (ip), and notable edema inhibition was achieved comparable to aspirin (100 mg/kg, ip). A notable inhibition of inflammation and arthritic nodules was noticed (Awuchi 2019). Antiarthritic potential of OS was also studied on formaldehyde-induced arthritis in rats, and marked improvement in the arthritic condition was achieved as result on daily application of OS fixed oil for 10 days ip. The fixed oil diminished the aroused paws up to a great extent (Singh et al. 2012a). The sequential release of mediators in turpentine oil-induced arthritis and carrageenan-induced paw edema, i.e., serotonin and histamine in earlier, kin in middle, and prostaglandins in later phase, is well inhibited by the fixed oil constituents of OS. These abovementioned mediators are inhibited by OS, so it is natural that fixed oil could inhibit inflammatory reaction involving different inflammatory mediators. The conclusion from the above study suggests potentially useful antiarthritic activity of fixed oil from OS (Pattanayak et al. 2010).

4.4.9 Antiulcer Activity

Antiulcer potential of *OS* was appraised on animals with induced gastro-intestinal ulcer. Fixed oil of *O. sanctum* possesses significant antiulcer and anti-inflammatory activity through antagonistic effect on the several chemicals and mediators responsible for gastric ulceration (Kousik and Baldev 2012). The management of gastric ulceration induced by NSAIDs, ethanol, histamine, reserpine, serotonin, and stress is accomplished due to lipoxygenase inhibitory, histamine antagonist, and antisecretory effects of the fixed oil extracted from OS (Kelm et al. 2000; Pattanayak et al. 2010). Drug possessing anti-inflammatory and antiulcer activity having null ulcerogenic effect has great importance in this modern era of allopathic medicine. A well-illustrated flowchart signifying the cause and management of gastric ulcer explains the marked antiulcer activity of OS shown in Fig. 4.3 (Singh and Majumdar 1999).

4.4.10 Anthelmintic Activity

The essential oil from *Ocimum sanctum* has extensive anthelmintic property. In the *Caenorhabditis elegans* model when tested in vitro, eugenol showed an ED50 of 62.1 μg/mL. Several studies have revealed essential oil of OS as the putative anthelmintic principle (Kousik and Baldev 2012). Ursolic acid found in tulsi has more efficient anthelmintic potential as compared to albendazole. It was found that ursolic acid paralyzes and kills worms at great extent (Inbaneson et al. 2012).

4.4.11 Anti-inflammatory Activity

Anti-inflammatory potential of OS is appraised in rats via carrageenan-induced paw edema, and it was found that 3 mL/kg fixed oil of OS when administered intraperitoneally inhibits edema due to true anti-inflammatory action not due to counter-irritant property (Singh et al. 1996). The anti-inflammatory effect of oil is found independent on pituitary adrenal axis when evaluated in adrenalactomized and nonadrenalactomized rats (Mondal et al. 2009). A significant inhibitory action on various mediators of inflammation like histamine, serotonin, bradykinin, and prostaglandins was ascertained when tested on inflammatory mediator-induced edema. *Ocimum sanctum* exhibits anti-inflammatory potential via inhibition of both COX and LOX pathways of arachidonic acid metabolism (Singh et al. 2007). The relative contribution of OS fixed oil toward COX inhibition and LOX inhibition and inhibitory effect of antihistamine in arachidonic acid-induced paw edema were evaluated (Singh et al. 2007). The fixed oil of OS shows an excellent edema inhibitory potency than indomethacin or caffeic acid, a potent COX and lipooxygenase inhibitor. Thus the above results highlight the potent anti-inflammatory activity of *Ocimum sanctum* (Singh and Chaudhuri 2018).

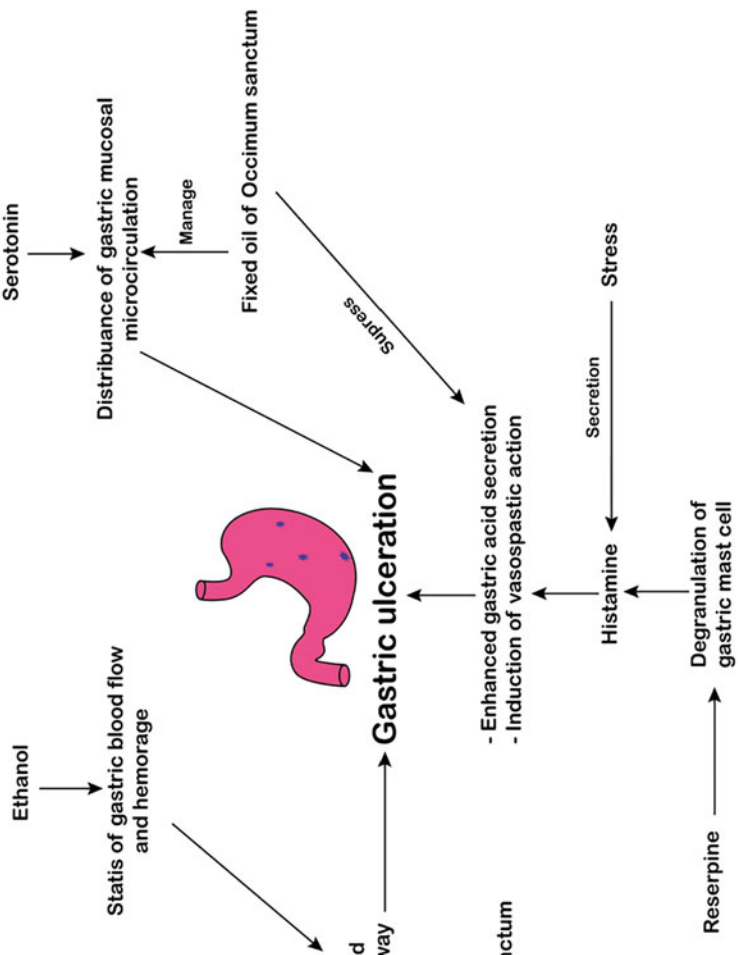

Fig. 4.3 Flowchart showing the antiulcer potential of tulsi

4.4.12 Analgesic Activity

Pain is a distressing feeling often marked as cardinal signs of inflammation. The analgesic potential of OS fixed oil was estimated by means of chemical and thermal induced pain model. These include acetic acid writhing test and formalin-induced paw licking test, the formalin-induced model as a chemical pain model while tail flick, tail clip, and tail immersion method as a thermal-induced pain model (Kaur 2014). For the thermal induced pain model, response time of rat to pull back its tail from hot water or a hot wire is noted in tail immersion or tail flick model, while in tail clip method, response time to extricate the clip was noted. The insufficient elevation of pain threshold of rat toward heat emphasizes the non-central action of OS fixed oil. Thus, to differentiate the central and peripheral analgesia potency of OS fixed oil, acetic acid-generated writhing response in rat was used. Ethyl acetate extract of OS exhibited extensive inhibition of writhing persuaded by acetic acid and formalin-induced paw licking in dose-dependent manner. Therefore analgesia activity of OS oil appears to be superficially facilitated and achieved by additive inhibitory effects of histamine, acetylcholine, and prostaglandin (Prakash and Gupta 2005; Pandey et al. 2014).

4.4.13 Antipyretic Activity

Prostaglandins (PGE) mediate pyrogenic fever; hence inhibition of prostaglandin synthesis results in the antipyretic action of drugs. Various anti-inflammatory drugs including NSAIDs are supposed to inhibit prostaglandin synthesis. The antipyretic power of the OS has been tested with typhoid, a paratyphoid vaccine A/B that used pyrexia in mice (Kelm et al. 2000). Intra-peritoneal administration of fixed oil of OS (3 mL/kg) reduced the pyretic response in rats as compared to aspirin. The fixed oil from *Ocimum sanctum* is moreover found to impede the synthesis of prostaglandin emphasizing its antipyretic potential (Balakumar et al. 2011; Kaur 2014).

4.4.14 Anticancer Activity

Extensive studies, experiments, and clinical studies prove that OS holds a prodigious potential not only as prevention but moreover within the treatment of a wide range of cancers and tumors in human. The chemoprotective and antitumor therapeutic efficacy can be elucidated by potential of enzyme to elucidate activity and signal transduction pathways modulating strength as well as antioxidant, antiproliferative, anti-invasive, immunomodulatory, antiangiogenic, and anti-metastatic properties of OS. It plays a pivotal role in treatment and prevention of cancer by altering the several carcinogen metabolizing enzymes like CYP450, CYB5, aryl hydrocarbon hydroxylase (Karthikeyan et al. 1999a), etc., antioxidant enzymes such as CAT and SOD, and GSH and GSH-related enzymes like GST and GSH-Px (Tables 4.4 and 4.5). Studies have revealed that extract of OS mediates a notable decrease in volume

Table 4.4 In vitro studies for anticancer potential of *O. sanctum*

Phytoconstituents tested	Cancer cell lines	Anticancer effects	Mechanism of action	Concentration of phytoconstituents	References
Ethanolic extract of leaves	A549 human non-small-cell lung carcinoma	Cytotoxicity	↑SUB-G1 ↑Apoptosis ↑Cyt.c ↑Caspase-9 ↑Bax ↓pAKT ↓pERK	25–200 μg/mL	Karthikeyan et al. (1999a)
Ethanolic extract of leaves	Mouse Lewis lung carcinoma	Decrease cell viability and inhibition of cell adhesion and invasion	↓MMP-9	25–100 μg/mL	Niture et al. (2006)
Ethanolic extract of leaves	HFS-1080 human fibrosarcoma	Cytotoxicity	↑Lipid peroxidase ↓GSH	50–400 μg/mL	Magesh et al. (2009)
Ethanolic and aqueous extracts of leaves	HT29 human colon cancer	Attenuation of alkylation-induced carcinogenesis	↑MGMT ↑GSTP1 proteins and mRNAs	10–20 μg/mL	Kim et al. (2010)
Vicenin; vicenin + docetaxel	PC-3, DU-145, and LNCaP human prostate carcinoma	Induction of antiproliferative, antimigration, and antiangiogenic effects	↑Apoptosis ↑E-cadherin ↓CDK4 ↓hTERT ↓c-Myc ↓Cyclin D1 ↓VEGF ↓Cyclin B1 ↓PCNA ↓Bax ↓Bcl-2 ↓G2/M	50 μmol/L	Nagaprashantha et al. (2011)

Table 4.5 In vivo studies for anticancer potential of *O. sanctum*

Phytoconstituents tested	Animal model (chemically induced cancer models)	Anticancer effect	Mechanism of action	Dose	Route of administration	Duration	References
Leaf paste	B[a]P-induced gastric carcinogenesis in male mice and 3′-MeDAB-induced hepatocarcinogenesis in male Wistar rats	Prevented the occurrence of tumor in the stomach and liver		600 mg/g	Diet, ad libitum	10–14 weeks	Aruna and Sivaramakrishnan (1992)
Ethanolic extract of leaves	DMBA-induced skin papillomagenesis in male Swiss albino rat	Reduction of incidence, multiplicity, and cumulative number of papilloma	↑GSH ↑GST	5 mg/kg	Topical	2–15 weeks	Prashar et al. (1994)
Ethanolic extract of leaves	MNNG-induced gastric carcinogenesis in male Wistar rat	Suppression of incidence of gastric carcinoma	↑Cyt. C ↑Bax ↑Caspase-3 ↓PCNA ↓GST-P1 ↓CK ↓VEGF ↓Bcl-2	300 mg/kg	Orally	2 times per week for 24 weeks	Manikandan et al. (2007)
Isolated seed oil	MCA-induced fibrosarcoma in Swiss albino mice	Enhanced survival rate; suppression of tumor volume and its incidence	↑GSH ↑SOD ↑GST ↑CAT ↓MDA	100 mg/kg	Orally	15 weeks	Prakash et al. (1999)

(continued)

Table 4.5 (continued)

Phytoconstituents tested	Animal model (chemically induced cancer models)	Anticancer effect	Mechanism of action	Dose	Route of administration	Duration	References
Ethanolic extract of leaves + extract of leaves of neem	MNNG-induced gastric carcinogenesis in male Wistar rat	Suppression of incidence of gastric carcinoma	↑TBARS ↑LOOH ↑CD ↑PC ↑Cyt. C ↑Bax ↑Caspase-3 ↓PCNA ↓GST-P1 ↓Bcl-2 ↓VEGF ↓CK	150 mg/kg	Orally	3 times per week for 26 weeks	Manikandan et al. (2008)
Fresh leaf juice	DMBA-initiated and croton oil-promoted multiorgan carcinogenesis in Swiss Webster mice	Exhibit complete protection against liver and skin tumor	N/A	Not specified	Topical	3 times a week for 20 weeks	Serrame (1995)
Fresh leaves paste; aqueous and ethanolic extract of leaves	DMBA-induced buccal pouch carcinogenesis in male Syrian golden hamsters	Attenuated the incidence of papilloma and carcinoma with increased survival rate	N/A	1 g/kg (paste) 30 mg/kg 300–800 mg/kg (extract)	Topical Topical Orally	16 weeks	Karthikeyan et al. (1999b)

Ethanolic extract of leaves	MCA-initiated; DMBA-initiated; AFB_1-initiated; TPA-promoted skin tumorigenesis in female Swiss albino mice	Decreased skin tumors with improvement of histological appearance	↑GST; ↑QR; ↑IL-1β;↑TNF-α; ↓GGT; ↓GST-P; ↓LPO;↓GSH; ↓AHH; ↓ERD; ↓ODC	100 μL/mouse	Topical	2 times per week for 24 weeks	Rastogi et al. (2007)
Eeugenol	DMBA-initiated and croton oil-promoted skin carcinogenesis in female Swiss albino mice	Inhibited the number of papilloma	↓Lipid peroxidation; ↓SOD	2 mg/mouse	Topical	6 weeks	Bhattacharyya and Bishayee (2013)
Xenograft cancer models							
Ethanolic extract of leaves	C57BL/6 mice inoculated with Lewis lung carcinoma cells	Decreased tumor volume and weight		50 and 100 mg/kg	Intraperitoneally	Every other day for 18 days	Magesh et al. (2009)
Aqueous and ethanolic extracts of leaves	Male Swiss albino mice xenografted with sarcoma—180 cells	Reduced tumor volume with increase in survival		800–1200 mg/kg	Orally	3 times per week for 4 weeks	Karthikeyan et al. (1999a)
Alcoholic aqueous leaf extract	Male C57BL and Swiss albino mice injected with $B_{16}F_{10}$ murine melanoma cells and/or irradiated	Attenuated tumor volume and improved survival	↓Chromosomal aberration; ↑GSH; ↑GST	200 mg/kg	Orally	Once	Monga et al. (2011)

(continued)

Table 4.5 (continued)

Phytoconstituents tested	Animal model (chemically induced cancer models)	Anticancer effect	Mechanism of action	Dose	Route of administration	Duration	References
Ethanolic extract of leaves	Female C57BL/6 mice injected with Lewis lung carcinoma cells	Inhibited the formation of metastatic lung nodules and lung weight	↑SOD; ↑CAT; ↑GSH-P_x	50 and 100 mg/kg	Intraperitoneally	Every other day for 18 days	Kim et al. (2010)
Vicenin-2; vicenin-2 + docetaxel	Athymic nude nu/nu mice transplanted with PC-3 prostate cancer cells	Reduced tumor weight, tumor cross-sectional area, and angiogenesis	↓Ki-67; ↓CD31; ↑E-cadherin; ↑PARP; ↓pAKT; ↓pRB; ↓PCNA; ↓cyclin D1; $VIGF_1R$; ↓fibronectin	1 mg/kg (vicenin-2), 0.01 mg/kg (docetaxel)	Orally	Every other day for 8 weeks	Nagaprashantha et al. (2011)
Methanolic extract of leaves	Swiss albino mice inoculated with Ehrlich ascites carcinoma cells	Reduced tumor volume and tumor weight and prolonged survival	Hematological alterations	50 mg/kg	Intraperitoneally	Once daily for 9 days	Saiful Islam et al. (2011)

of tumor, tumor cell size, rise in body weight, and survival rate of mice having sarcoma-180 solid tumor when administered 200 mg/kg, po (Singh et al. 1996; Kelm et al. 2000).

4.4.15 Antiviral Activity

Viral infections are the major causes of devastations for human and animal health worldwide. Being an obligate intracellular parasite, any intervention will affect the cellular metabolism of the host; thus, developing an antiviral drug is a great challenge for mankind (Tang et al. 2012). This has diverted attention of the researchers and scientists to develop antiviral drug from the native traditional plant (Cohen 2014; Kaur 2014). Several studies have revealed the antiviral property of *Ocimum sanctum*. Evaluation of antiviral potential against orthomyxovirus and paramyxovirus has shown the significant viral infection inhibitory potential of tulsi (Mohan et al. 2011). The ethanolic extraction of the air part of tulsi contains details of the content of flavonoids and polyphenolic compounds; these are further described before having the same antimicrobial properties. In silico experiments of phytochemicals such as SARS-CoV-2 primary protease inhibitors suggest that flavonoids and polyphenolic chemicals of tulsi, especially luteolin-7-*O*-glucuronide and chlorogenic acid, can bind by combining the active residual Cys145 of the COVID-19 main protease and inhibiting the immune system (Mohapatra et al. 2020). OS extract has shown a preventive degree against coronavirus due to its potential to restrain replication of coronavirus bolstered with its immunomodulatory feature and angiotensin-converting enzyme (ACE) II inhibiting potency (Varshney et al. 2020).

Studies show chemicals from OS like methyl eugenol, oleanolic acid, and ursolic acid which have a strong binding effect on both spike glycoprotein and RNA polymerase of novel coronavirus. These compounds showed better binding energy than the positive control (STGYC and remdesivir) (Kumar 2020).

4.4.16 Antimicrobial Activity

Ocimum sanctum has been described for its antimicrobial potency against Gram-positive and Gram-negative bacteria. The results have shown that the essential oil and extract of leaves (aqueous, alcoholic, and chloroform) are equally effective against both strains of bacteria (Cohen 2014; Kaur 2014). Tulsi's antibacterial activity was evaluated against bacteria responsible for tooth decay, i.e., *Streptococcus mutans*, and it was confirmed that mouthwash with tulsi is equally effective as 0.2% chlorhexidine and listerine (Prakash and Gupta 2005; Singhal et al. 2011). Flavonoid content of OS showed significant efficacy against UTI-causing bacterial strains, e.g., *Escherichia coli*, *Proteus*, *Klebsiella pneumoniae* (gram –ve), *Staphylococcus aureus*, and *Staphylococcus cohnii* (gram +ve) using disk diffusion method. Orientin and vicenin synergistically show significant inhibition on bacterial

growth compared to individual inhibitory potential of flavonoids (Prasannabalaji et al. 2012).

4.5 Clinical Efficacy of Tulsi [Clinical Study]

Tulsi has been reported beneficial for several disorders and diseases. Despite of abundant availability and extensive antiquity of traditional use of *Ocimum sanctum*, comparatively limited human interventions study has been done on clinical efficacy (Grover et al. 2002; Ghorbani 2013). Plethora of bioactive secondary metabolite constituents of tulsi act alone or synergistically to inhibit the inflammatory ailments, and regular consumption of tulsi assists in normalizing numerous metabolic disorders. A summary and critically evaluated human clinical trials enhance and potentiate the tulsi's efficacy against various metabolic disorders, viral infections, neurocognition, and immunomodulation (Gupta et al. 2014; Ahirwar et al. 2018) which are well illustrated via Tables 4.6 and 4.7.

4.6 Nutritional Value

In addition to secondary metabolites, *O. sanctum* also contains several components which are of great nutritional values (Pattanayak et al. 2010; Kaur 2014). The herb is very low in calories. Fresh basil leaf is prodigious source of vitamin A; it is found that 175% of daily required dose is fulfilled by intake of 100 g fresh basil leaf. Basil herb contains a weighty amount of minerals like potassium (K), manganese (Mn), copper (Cu), and magnesium (Mg). Basil leaves are extremely rich in iron. 100 g of fresh leaves contains 3.17 mg of iron. Various researches have revealed the following components which are of great nutritional values and represented in Table 4.8 (Kumar et al. 2010; Prasannabalaji et al. 2012).

4.7 Conclusion

OS is widely cultivated from the beginning of human civilization for its medicinal importance and as an herbal tea. Ayurveda, Siddha, and Unani described medicinal properties of this plant in the traditional system of medicine. The herbal drug remains devoid of side effects, so researches on the herbal plant were increasing and scientific research showed OS has huge biological potential. Research showed OS has various secondary metabolite, vitamins, and minerals. These phytoconstituents elucidate various pharmacological effects. Tulsi has significant pharmacological potential and has been clinically proved for both its beneficial application and effectiveness. The various clinical trials are completed, and some are still going on to establish its efficacy for chronic disease. However, some marketed product is also available as nutraceutical products.

Table 4.6 A summary and critically appraise human clinical trials of *Ocimum sanctum*

Clinical domain	Year of study	Study design	Tulsi extract (phytoconstituents)	Participants (age group)	Dosage	Duration	Outcomes	References
Metabolic disorders	1964	Clinical trail	Whole plant decoction, powder	10 adults T2DM	14 g/day	12 weeks	Reduced blood glucose level in 9 participants	Kochhar et al. (2009)
	1986	Randomized placebo controlled cross-over	Fresh juice (75% Tulsi)	20 adults (45–64 years) Hypertension	3 mL/day	10 days (+5 days wash-out)	Significant decrease in BP	Matsukawa et al. (1987)
	1986	Randomized placebo controlled cross-over	Fresh juice (75% Tulsi)	16 adults (45–65 years) Hypertension	30 mL 2 times/day before meal	12 days	Significant lower in BP by 25%	Matsukawa et al. (1987)
	1996	Randomized, single-blind, placebo-controlled cross-over	Tulsi powder leaves	40 adults (41–65 years) T2DM	2.5 g/day in morning before meal	5 weeks (+5 days wash out)	Significant decrease in fasting glucose, PP glucose and urine glucose	Agrawal et al. (1996)
	1997	Clinical trial controlled group	Tulsi powder leaves	27 adults (45–65 years) T2DM/MeS)	1 g/day in morning before meal	4 weeks	Improvement in lipid profile, glycated proteins (HbAlc), blood sugar, and UA	Rai et al. (1997)

(continued)

Table 4.6 (continued)

Clinical domain	Year of study	Study design	Tulsi extract (phytoconstituents)	Participants (age group)	Dosage	Duration	Outcomes	References
	2009	Randomized, clinical trials	Tulsi leaves powder	90 male adults (40–60 years) T2DM/MetS	2 g/day	12 weeks	Improved T2DM symptoms, decrease in polydipsia, polyphagia, and BP	Kochhar et al. (2009)
	2010	Placebo controlled clinical trial	Aqueous extract of tulsi leaves	40 adults (45–55 years) T2DM	500 g/day	8 weeks	Significant improvement in lipid profile	Dineshkumar et al. (2010)
	2012	Randomized placebo-controlled clinical trials	Tulsi leaves + glibenclamide drug	60 adults (30–65 years) T2DM	300 mg/day tulsi + 5 mg glibenclamide	13 weeks	Significant decrease in fasting blood and PP glucose, reduce HBA1c	Somasundaram and Manimekalai (2012)
	2012	Randomized, clinical trial	Aqueous tulsi leaves	100 adults (≥40 years) MetS	5 mL/2 days before meal	12 weeks	Improvement in lipid profile, BP, and fasting blood glucose	Jamshidi and Cohen (2017)
	2012	Randomized, double-blind, placebo-controlled cross-over	Ethanolic extract of tulsi	22 healthy adults (22–37 years)	300 mg/day before food	4 weeks (+3 week wash-out)	Reduction in lipid profile in 6 participants	Jamshidi and Cohen (2017)

	2012	Clinical trial	Whole tulsi plant	5 adults (60–80 years) Psychosomatic	3 g/2 days	12 weeks	Significant improvement in lipid profile	Jamshidi and Cohen (2017)
	2013	Randomized, single-blind parallel group	Tincture from tulsi	200 adults Gouty Arthritis	10 drops 3 times/day	12 weeks	Significant reduction in serum uric acid	Ahmad et al. (2013)
	2014	Clinical study case report	Fresh tulsi leaves	3 adults T2DM	Fresh leaves 3 times daily	5 weeks	Significant decrease in blood glucose reaching near normal level	Jamshidi and Cohen (2017)
	2015	Clinical trial controlled parallel group	Tulsi leaves powder	30 adults T2DM	2 g/day	2 weeks	Significant decrease in fasting and PP blood glucose level	Ahangarpour et al. (2017)
	2016	Randomized controlled clinical trial	Tulsi leaves capsule	40 male adults (45–55 years) T2DM	3 g/day before meal	6.5 weeks	Significant decrease in PP glucose and fasting blood glucose	Chauhan (2017)
	2016	Randomized parallel group clinical trial	Tulsi leaves capsules	30 adults (17–30 years) Obesity	250 mg/day 2 times daily before meal	8 weeks	Improvement in lipid profile except TC, BMI, TG, and IR	Satapathy et al. (2017)

(continued)

Table 4.6 (continued)

Clinical domain	Year of study	Study design	Tulsi extract (phytoconstituents)	Participants (age group)	Dosage	Duration	Outcomes	References
Immunomodulation	1983	Open clinical trial	Aqueous tulsi leaves tablet	20 adults Asthma	500 mg 3 times/day	1 week	Relief within 3 days, improvement in vital capacity	Mayank and Vikas (2014)
	2011	Randomized, double blind, placebo-controlled cross-over	Ethanolic extract of tulsi leaves	22 healthy adults (22–37 years)	300 mg/day	4 weeks (+3 weeks wash-out)	Increase in interferon-γ, cytokine level, and interleukin-4 level	Jamshidi and Cohen (2017)
	2014	Randomized, placebo-controlled clinical trial	Ethanolic extract of tulsi leaves in Bar	30 healthy adults (18–30 years)	1 bar 2 times/day (1000 mg tulsi)	2 weeks	Loss of fatigue and increase in physical performance, less increase in lactic acid	Martins et al. (2018)
Neurocognition	2008	Clinical trials	Ethanolic tulsi leaves capsules	35 adults with GAD (18–60 years)	200 mg 2 times daily after meals	8 weeks	Reduction in stress, anxiety, and depression	Bhattacharyya et al. (2008)
	2012	Clinical trials	Powder of whole tulsi plant	24 adults (60–80 years) Psychosomatic	3 g two times per day	12 weeks	Stress reduction, significantly lowered biological age score	Verma et al. (2012) and Jamshidi and Cohen (2017)

	2012	Randomized, double-blind, placebo controlled clinical trial	OCIBEST Whole plant capsule	150 adults (18–65 years) Stress	400 mg 3 times/day after meal	6 weeks	Reduction in stress related symptoms: fatigue, sleep, and sexual problems	Jamshidi and Cohen (2017)
	2015	Randomized, double-blind, placebo controlled clinical trial	Ethanolic tulsi leaves capsules	40 healthy adults (18–30 years)	300 mg/day before meal	4 weeks	Improved memory power only after 15 days, cognitive flexibility	Jamshidi and Cohen (2017)
Viral infections	1983	Randomized clinical trial parallel controlled	Aqueous extract of fresh tulsi leaves	14 adults Viral encephalitis	2.5 g 4 times/day	4 weeks	Increased survival rate as compared to steroid	Joshi (2014)
	1986	Clinical trial	Aqueous extract of fresh tulsi leaves	20 case, (10–60 years) Viral hepatitis	10 g daily	2 weeks for mild cases, 3 weeks for severe cases	Improvement in symptoms within 2 weeks	Jamshidi and Cohen (2017)

Table 4.7 Completed and ongoing clinical trials

S. no.	Title	Condition	Intervention	Status	Result	Location	Reference
1.	Comparative evaluation of antiplaque and antigingivitisEfficacy of *Ocimum sanctum* (Tulsi) extract	Periodontal diseases, gingivitis, periodontitis	*Ocimum sanctum*, chlorhexidine gluconate, propylene glycol	Completed	N/A	GCD Indore, Indore, Madhya Pradesh, India	NCT03474146 (2018)
2.	Effect of Tulsi (*Ocimum sanctum*) on biochemical parameters in young overweight and obese subjects	Obesity	Drug: Tulsi (*Ocimum sanctum* Linn.) capsules	Completed	N/A	All India Institute of Medical Sciences, Bhubaneswar, Odisha, India	Satapathy et al. (2017)
3.	Trial of an herb and mineral combination product on fasting glucose in adults at risk for developing diabetes	Prediabetes	Dietary supplement: herb and mineral combination product, dietary supplement: placebo	Completed	N/A	• Radiant Research, Chicago, Illinois, United States • Central Kentucky Research Associates, Lexington, Kentucky, United States • Quest Research Institute, Bingham Farms, Michigan, United States • Radiant Research, Cincinnati, Ohio, United States • Providence Health Partners Center for Clinical Research, Dayton, Ohio, United States • Mountain View Clinical Research, Greer, South Carolina, United States	Zhang et al. (2015)

4.	Tulsi consumption and its effects on cognition, stress and anxiety	Cognitive change	Drug, *Ocimum sanctum*; drug, placebo	Completed	N/A	Narayana Hrudayalaya Limited, Mazumdar Shaw Multispecialty Hospital, Bangalore, Karnataka, India	Chong et al. (2019)

Table 4.8 Nutritive value per 100 g (source: USDA National Nutrient data base)

Principle	Nutrient value	Percentage of RDA
Protein	3.15 g	6%
Dietary fiber	1.60 g	4%
Total fat	0.64 g	2%
Carbohydrates	2.65 g	2%
Energy	23 Kcal	1%
Phytonutrients		
Lutein-zeaxanthin	5650 μg	–
Beta-carotene	3142 μg	–
Beta-cryptoxanthin	46 μg	–
Vitamins		
Vitamin K	414.8 μg	345%
Vitamin A	5275 IU	175%
Vitamin C	18 mg	30%
Vitamin E	0.80 mg	5%
Folates	68 μg	17%
Pyridoxine	0.155 mg	12%
Niacin	0.902 mg	6%
Riboflavin	0.076 mg	6%
Pantothenic acid	0.209 mg	4%
Thiamin	0.034 mg	2.5%
Minerals		
Manganese	1.15 mg	57%
Copper	385 mg	43%
Iron	3.17 mg	40%
Calcium	177 mg	18%
Magnesium	64 mg	16%
Zinc	0.81 mg	7%

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Nigella sativa: Its Ethnobotany, Phytochemistry, and Pharmacology

5

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Abstract

Black seed (*Nigella sativa*) plant belongs to the Ranunculaceae family native to the Middle East, India, and Pakistan and also the neighboring countries. It is an annual flowering plant. Several medicinal uses have been reported. This plant has a historical and religious background that emerges as a miracle. The holy books Quran and Bible mention this plant that it can cure most of the diseases. This medicinal plant is rich in bioactive compounds and is globally used for food purposes or traditional medicine. A database collection from like Science Direct, Medline, PubMed, Scopus, EBSCO, and SID. Numerous therapeutic effects were reported like antioxidant, anti-inflammatory, antihypertensive, anti-diabetic, rheumatoid, anti-arthritic, digestive disease, cardiac disease, anti-cancer, reproductive disease, CNS diseases, and others. Several constituents are present in the plant, but among these thymoquinone (TQ) is the most important; several types of research in vivo and in vitro confirmed the various pharmacological activities.

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This valuable plant is used for the development of a new formulation to cure several diseases.

Keywords

Nigella sativa · Thymoquinone · Bioactive · In vivo and in vitro · Pharmacological activities

5.1 Introduction

From the last two decades, compatible and alternative medicine takes a place among the population worldwide for curative, preventative, and treatment of disease (Cooper 2004). According to the WHO world, more than three fourth populations rely on herbal medicine in primary health care; poor people are not able to effort allopathic medicine. Uses of medicinal plants for the treatment of various illnesses have been practiced for many centuries in the indigenous system. *Nigella sativa* is one among them (Al-Ghasham et al. 2008). Several traditional medicine systems like Unani and Tibb, Ayurveda, and Siddha have admired *N. sativa*. Articles regarding the seeds of black cumin (*N. sativa*) were revealed in the tomb of Egyptian Pharaoh Tutankhamen (Zohary et al. 2015). *N. sativa* Linn. is an astonishing herb that has an abundant historical and religious background among the medicinal plants (Goreja 2003).

This plant had may be used in the practice of the ancient Egyptians, found in documents as a panacea (cure for problems and diseases). Some religious and medical texts have discussed its medicinal importance about the seeds of this plant. "Melanthion" referred to by Hippocrates and Discords was identified and described by Linnaeus in 1753 (Padhye et al. 2008).

Prophet Muhammad (PBUH) stated the *N. sativa* is a remedy for every disease except death; seeds of this plant are used by Prophet Muhammad with honey syrup for the therapeutic purpose (Bakathir and Abbas 2011). The name of the plant is referred to in Islamic countries as Habbatus Sauda, Alhabahat Alsawda, and Alkamoun Alaswadin on references to the color of seeds, mentioned in Islamic literature as healing medicine. In the holy book Bible, *N. sativa* was described as "Curative black cumin" (Isaiah 28:25, 27 NKJV) (Padhye et al. 2008). IbniSina referred the seeds of the plant "stimulate the body's energy and helps recovery from fatigue" in famous book *The Canon of Medicine* (Zaid et al. 2012). The historical and religious background of this plant came as a miracle that has several pharmacological properties.

Researcher focusing to develop new formulation from natural products encouraged due to it considered that, of the total 300,000 herbal spices globally floated, only 15% have been traversed of their pharmacological strength (De Luca et al. 2012).

Herbal medicine, either plant extract or plant-derived compound formulation, since the last centuries is used for the treatment of several diseases like cancer,

diabetes, cardiovascular disease, and oxidative dysfunction and other diseases and is also preferred because of fewer side effects and easily available (Rocha et al. 2005). The seeds of the plant are prescribed for health problems like headache, nasal congestion, and toothache, for internal worms, and for normal and regular menstruation and also enhance the milk production (Goreja 2003) by ancient Egyptian and Greek physicians.

N. sativa (NS) or black seed belonging to the family Ranunculaceae is an annual flowering dicotyledonous plant, native of the Mediterranean and neighboring countries of Pakistan and India, thus becoming a household traditional medicinal plant in the region.

Plants part are the component of the human diet, from ancient it has a practice in the Middle East, in daily diet uses as a spice and preservative (Gali-Muhtasib et al. 2006; Ali and Blunden 2003). Over the last five decades, several kinds of research have been done and reported the therapeutic importance of NS seeds; animal studies have revealed its anti-inflammatory, anti-bacterial, anti-histamine, anti-diabetic, anti-cancer, and antihypertensive activity (Ali and Blunden 2003).

The nephrotoxicity and hepatotoxicity may be because of disease or chemicals cured by the use of the crude extract of the seeds.

Seed oil has properties to reduce blood pressure and increase respiration. From an animal studied, it reported an increase in both packed cell volume (PCV) and hemoglobin (Hb) and decrease in the concentration of cholesterol, triglycerides, and glucose. The adverse effects on liver or kidney function have not been found taken either from seed extracts or oil of seeds; a low degree of toxicity is found in seed extract (Ali and Blunden 2003). A beneficial effect of thymoquinone and seeds might be related to cytoprotective and anti-oxidant effects.

Thymoquinone is the main constituent of the *N. sativa* that is responsible for the most therapeutic effects. The important components like thymohydroquinone (THQ), dihydro-thymoquinone (DHTQ), p-cymene, carvacrol, α-thujene, thymol, t-anethole, β-pinene, and γ-terpinene are present in *N. sativa* seed oil.

Seeds are used as a flavoring agent in pickles and bread because studies reported very less toxicity (Ahmad et al. 2013). Seeds and seed oil of this plant have more medicinal value as compared to the whole plant; different parts are used after little processing as a single and compound drug. Nutritional value is because of the availability of a considerable amount of vegetable protein, fiber, minerals, and vitamins. A nutritional composition was mentioned from various sources including protein (20–85%), fat (38.20%), fiber (7–94%), and carbohydrate (31.94%). Seeds contain fixed oil, essential oil, protein, alkaloids, and saponin.

Al-kindi discusses the use of seed in preparation of medicine for the treatment of skin irritation and insanity (Hosseinzadeh and Nassiri-Asl 2013). Ibn al-Baytar author reported the application of seeds against the paralysis and facial spasms, and Al-Qazwini describe its use to eliminate fleas and mosquitoes, pull out face freckles, for hair growth and straightening, to remove crawling insects, turn out the skin moles, and for the treatment of leukemia, leprosy, colds, and toothache (Bencheikh et al. 1987).

5.2 *Nigella sativa* (Synonym in Various Languages)

Hindi: Kalonji. English: black cumins, Love-in-a mist. Arabic: Habatut Barakah; Sonez; Habatut-sauda; Kamune-asvad. Sanskrit: Krishana-Jiraka. Persian: Siyadanah (Ahmad and Ghafoor 2007; Chevalier 1996).

5.3 *Nigella sativa* (Morphology)

N. sativa is a bushy plant that has a height of about 50–60 cm and it is self-branching. Two to three-cm-long leaves with linear segment arrange in the stem in pairs on both sides in an opposite manner, long leaves in the upper and small in the lower side. The session of flowering is March to May. Flowers have color either pale bluish or white, developed in branches in terminal position. It reproduces with itself and develops fruit capsules that have several seeds, have trigonal shape, and have a color becoming black as, when the capsules of the fruit matured, they open up and are exposed to the air. The shape of the seeds is triangular, its color is black, and its smelled like pungent with a considerable amount of oil (Al-Ghasham et al. 2008).

5.4 Characteristics of the Seeds and Powder

Seeds of the plant microscopically show these are small dicotyledonous, trigonus, angular, regulose-tubercular, and 2–3 in number and have a dimension 5 mm × 1–2- mm; externally they are black and inside white and have an aromatic odor and bitter taste. Seeds transverse section microscopically shows single-layered epidermis having elliptical, thick-walled cells, outside covered by a papillose cuticle and filled with dark brown contents. A thick-walled seed tangentially elongated made up of parenchymatous cells 2–4 layer below the epidermis it is present, after the layer of parenchymatous cells, a reddish-brown pigmented layer made up of thick-walled rectangular elongated or nearly columnar, elongated cells inner side. Oil globules are present in thin-walled cells of shape rectangular or polygonal in the endosperm. Microscopy of seed powder revealed brownish-black, parenchymatous cells and oil globules (Chevallier 2001).

5.5 *Nigella sativa* (Scientific Classification)

Kingdom: Plantae. Subkingdom: Tracheobionta. Superdivision: Spermatophyte. Order: Ranunculales. Family: Ranunculaceae—buttercup. Genera: *Nigella*. Species: *sativa*.

5.6 Cultivation and Collection

N. sativa, cultivated globally, is an annual herb in Asia region countries like India and Pakistan and other countries also cultivated in the winter session, the same pattern adopted as wheat cultivated. Areas of the land where crops like maize, green gram, or black grams are produced can be used for the cultivation of *N. sativa* after harvesting previous crops. Traditionally, it followed before sowing the seeds plowing the land at least 2–3 times to control the weed for good productivity. More plowing is required in heavy soils as compared to light soils. Germination on time taken place, if seeds are sowing 30 cm apart and should not be too much deepens in the land with quantity around per hectare will be 12–15 kg. Irrigation generally three to five times is needed in a stage like seeding, flowering, fruit formation, and seed development. Harvest early in the morning as the crop matures in April and May when fruits turn yellowish. Optimum drying must be required after harvesting has given trampling either with a tractor or proper thresher. Then after stored properly in bags or containers. Seeds are shattering because of late harvesting (Ahmad and Ghafoor 2007).

5.7 Chemical Constituents

Wide range of applications of medicinal use of this plant, detail phytochemical studies necessary to know every constituent qualitatively and quantitatively. Fixed oil has primarily contained unsaturated fatty acids like linoleic, arachidonic, eicosadienoic, and linolenic acid. Palmitic, stearic, and myristic acids are present in the oil, and saturated fatty acid is also present (Hajhashemi et al. 2004).

Gas chromatography-mass spectrometer has been used for the analysis of the essential oil of seeds; several components were characterized, but active pharmacological substances in volatile oil are thymoquinone, thymohydroquinone, dithymoquinone, and thymol. Thymoquinone dimerized form is dithymoquinone (Hajhashemi et al. 2004). Nigellone (dithymoquinone) is the only crystalline active constituent that has carbonyl group in fraction of the oil. Apart from these substances, the volatile oil of seeds has t-anethole, p-cymene, 4-terpineol, carvacrol, and longifolene. Total alkaloids are four reported in seeds such as nigellicine and nigellidine; both have an imidazole ring, whereas nigellimine and N-oxide of nigellimine have isoquinolines (Atta-ur-Rahman et al. 1985; Atta-ur-Rahman et al. 1995). Triterpene saponin Alfa isolated from *N. sativa* and α-heredin have an antitumor activity that has also been found (Kumara and Huat 2001a, Kumara and Huat 2001b). Three flavonoids are present (Merfort et al. 1997). Also kaempferol 3-glucoside and rutin and essential amino acids are present; glucose like rhamnose, xylose, and arabinose monosaccharide was found. Seeds have carotenes that convert to vitamin A in the liver, the source of irons, potassium, and calcium; more than 100 compounds identified in seeds of *N. sativa* and their structure were elucidated. The volatile oil of *N. sativa'*s main substance is TQ; its percentage is about 28–45% of the oil (Salem et al. 2010 Gali-Muhtasib et al. 2006; Ali and Blunden 2003).

Table 5.1 Chemical composition, including active principles, of *N. sativa* seed

S. No.	Class	Sub-class	Phytoconstituents	Reference
1	Fixed oil (32–40%)	Unsaturated fatty acids	Arachidonic, eicosadienoic linoleic, linolenic, oleic, and palmitoleic acid. Palmitic, stearic, and myristic acid. Beta-sitosterol, cycloeucalenol, cycloartenol, sterol esters, and sterol glucosides	Menounos et al. (1986)
2	Volatile oil (0.4–0.45%)	Saturated fatty acids	Nigellone, thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, α- and β-pinene, d-limonene, d-citronellol, p-cymene, and 2-(2-methoxypropyl)-5-methyl-1,4-benzenedio l6,16-18	Enomoto et al. (2001), El-Dakhakhny (1963), Ghosheh et al. (1999)
3	Proteins (16–19.9%)	Amino acids	Arginine, glutamic acid, leucine, lysine, methionine, tyrosine, proline and threonine, etc.	Babayan et al. (1978)
4	Alkaloids	–	Nigellicine, nigellidine, nigellimine-N-oxide	Atta-ur-Rahman et al. (1985, 1995)
5	Coumarins	–	6-Methoxy-coumarin, 7-hydroxy-coumarin, 7-oxy-coumarin	Atta-ur-Rahman et al. (1985, 1995)
6	Saponins	Triterpenes, steroidal	Alpha-hederin, steryl glucosides, acetyl-steryl-glucoside	Kumara and Huat (2001a, 2001b)
7	Minerals (1.79–3.74%)	–	Calcium, phosphorous, potassium, sodium and iron	Babayan et al. (1978)

Quinone content like TQ and its dimer dithymoquinone, thymohydroquinone (THQ), and thymol have revealed the pharmacological activities (Abukhader 2013). Several research reports of TQ in vitro and in vivo studied have shown several therapeutic effects such as analgesic, antihypertensive, lipid-lowering (Abdel-Fattah et al. 2000a, b; Zaoui et al. 2000), anti-inflammatory and anti-fungal (Mutabagani and El-Mahdy 1997; Khan et al. 2003a, b), anti-histaminic and anti-diabetic (Chakravarty 1993; Salem, 2005), and anti-cancer (Tariq 2008; Worthen et al. 1998; Jafri et al. 2010). The potential mechanism of anti-cancer activity is inhibition of nuclear factor-kappa (NF-κB) (Abukhader 2013; Sethi et al. 2008) (Table 5.1; Figs. 5.1 and 5.2).

Thymoquinone is the most active constituents found in black cumin having a percentage 18.4–24% of the volatile oil and thymol (El-Dakhakhny et al. 2000; Al-Saleh et al. 2006). Both chemical constituents revealed therapeutic effects when

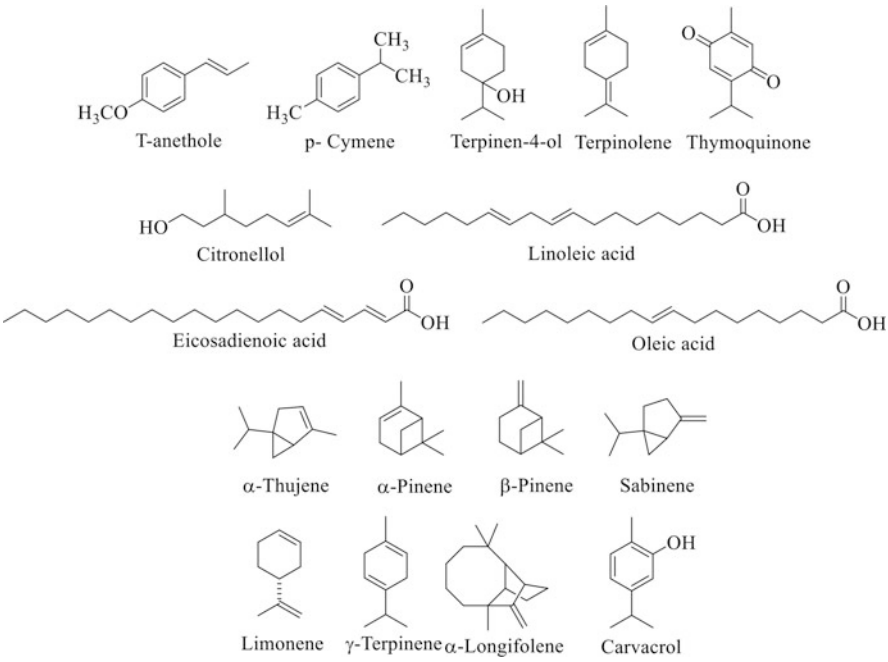

Fig. 5.1 Chemical structure of phytoconstituents

Fig. 5.2 *Nigella sativa* plant flowers and seeds

crude drugs are used in the indigenous medicine system. In the market, the demand increases for this medicinal plant, so it is important to maintain the quality of the raw material and its finished product.

Environmental factors have influence plant development and growth and also affect the standard and variation in the amount of herbal substance even when it is produced in the same country. The distribution of bioactive compounds varies with region of altitude. For example, concentration of rutin at middle altitude 600 m above sea level (masl) is higher than at high altitude (1150 masl) (Lumingkewas et al. 2015). The content of TQ and thymol in black cumin plant varies in the countries Ethiopia (3098.5 and 230.6 mg/kg), India (2362.8 and 201.16 mg/kg), Saudi Arabia (2250.6 and 133.88 mg/kg), Syria (1371.9 and 120.4 mg/kg), and Sudan (1274.6 and 113.40 mg/kg) (Al-Saleh et al. 2006).

For the cultivation of *N. sativa* in a tropical region, the limiting factor is climate especially air temperature. It is not possible to change the climate factor, but it can be modified as where the *N. sativa* plant cultivated; in tropical regions it is possible to alter the climate factor, for example, change the position from latitude to altitude or elevation. The surface air temperature of the earth is affected by multiple factors like the amount of radiation caught by the earth's surface, effects of land and sea, and also the slope of the region (Désalmand 1998). Climatic factor like air temperature affects the plant's metabolic process and rate of growth. It affects on germination, leaf formation, and initiation of reproductive organs. The physiological activities decline at high temperatures because of the inactivation of enzymes and other proteins (Pareek et al. 2010). In ingredient composition, *N. sativa* seeds contain 36–38% fixed oils, proteins, and alkaloids and 0.4–2.5% essential oils. Unsaturated fatty acids include the C20:2 arachidic and eicosadienoic acids.

By analytical technique GC-MS, essential oil was analyzed, several ingredients were reported, but the major ones were thymoquinone (27.8–57.0%), ρ-cymene (7.1–15.5%), carvacrol (5.8–11.6%), t-anethole (0.25–2.3%), 4-terpineol (2.0–6.6%), and longifolene (1.0–8.0%). Apart from these chemical constituents, seeds contain several esters; additionally, minute amount of alkaloids are present which belong to isoquinoline and pyrazole alkaloids. Substance like nigellimin and nigellimin-N-oxide belongs to class isoquinoline, and nigellidin and nigellicin belongs to pyrazole.

In the essential oil, identified TQ and THQ as primary substances have a percentage up to 50. Substance like p-cymene (40%) and pinene (up to 15%) along with other derivatives is present in very less amount such as carvacrol, 4-terpineol, limonene, carvone, and citronellol, and also 10% is fatty acid ethyl esters. In storage condition dithymoquinonene developed from thymoquinone along with oligocondensation product. The fatty oil present in seeds has abundant unsaturated fatty acids primarily linoleic acid (50–60%), oleic acid (20%), dihomolinoleic acid (10%), and eicosadienoic acid (3%). Saturated fatty acids also present a percentage of around 30% or less.

5.8 Therapeutic Importance

The therapeutic properties of *N. sativa* seed extract and other chemical substances are studied by several scientists. The research was performed and results were revealed. In vitro and in vivo studies have been done and reported the following therapeutic effects.

1. Antioxidant activity
2. Hepatoprotective activity
3. Anti-nephrotoxic activity
4. Anti-cancer activity
5. Anti-diabetic activity
6. Anti-microbial activity
7. Anti-parasitic activity
8. Anti-malarial
9. Anti-inflammatory and analgesic
10. Anti-nociceptive property
11. Anti-ulcer property
12. Anti-histaminic property
13. Effect on the cardiovascular system
14. Anti-hyperlipidemic effects
15. Effect on the gastrointestinal tract
16. Effect on the respiratory system
17. Effect on the nervous system
18. Effect on the immune system
19. Effect on the genitourinary system
20. Effect on the reproductive system
21. Effect on blood

5.8.1 Antioxidant Activity

Human disease and condition may be because of one region, the production of free radicals in the body. *N. sativa* in ancient claims the anti-oxidant properties that has been used in folk medicine. Research data published by several scientists confirmed that the essential oil of *N. sativa* has anti-oxidant properties. The chemical substances like TQ and others like anethole, carvacrol, and 4-terpinol have radical scavenging property. By chemiluminescence and spectrophotometer methods, thymol, TQ, and dimer-TQ had shown a free radical scavenging effect on the reaction producing reactive oxygen species like superoxide anion radical, hydroxyl radical, and singlet oxygen (Kruk et al. 2000). Houghton et al. reported TQ and fixed oil inhibit non-enzymatic peroxidation in ox brain phospholipid liposomes. Microsomal lipid peroxidation inhibition depends on concentration confirmed in in vitro study of TQ and tert-butyl thymoquinone (TBHQ).

5.8.2 Hepatoprotective Activity

Hepatotoxicity is due to altering the function of certain enzymes and also its level. The enzymes are serum glutamic-pyruvic transaminase (SGPT), glutathione (GSH) oxidant scavenger enzymes, catalase (CAT), and superoxide dismutase (SOD).

Animal studies, using isolated rat hepatocytes, and TQ protective action against hepatotoxin have been confirmed. Silybin is a known hepatoprotective agent used in this study to compare the TQ hepatoprotective activity, a clear mechanism not known but may be protected by intracellular glutathione (GSH). Disease condition like ischemia-reperfusion on the liver can also be a cure (Yildiz et al. 2008).

5.8.3 Anti-nephrotoxic Activity

Nephrotoxicity is induced by cisplatin single drug or combination of cisplatin and gentamycin drugs. Nephroprotective effects are observed when seed extract is taken with cysteine, vitamin E, and *Crocus sativus* and in combination with *N. sativa* seed oil for the same effects. Probably the nephrotoxic effects are due to anti-oxidant properties (Ali 2004). A known disease is Fanconi syndrome (FS) the symptom of which is a decline in the level of electrolyte, glucose, and organic acids and high serum creatinine with low clearance rate. This disease is produced when using the drug ifosfamide for the treatment of cancer. Administration of TQ before and during the use of drugs with drinking water had shown a positive change in biochemical parameters (Badary et al. 1999).

5.8.4 Anti-cancer Activity

Anti-cancer activity of the crude extract of the seeds reported by Salomi et al. has shown very strong cytotoxic effects on cancer cells of Ehrlich ascites and Dalton's ascites. In the cancer cell of the breast, it had shown that the combination of H_2O_2 and alcoholic extract of *N. sativa* inactivates MCF-7. Another study using animal male albino rats induced with fibrosarcoma by 20-methylcholanthrene, in vivo and in vitro studied, investigated the effect of TQ and β-elemene and found inhibition on the growth of the tumor. The expected mechanism behind this may be anti-oxidant effects and interference with DNA synthesis along with detoxification (Badary and Gamal El-Di 2001; Gali-Muhtasib et al. 2006).

Anti-cancer activity of ethanolic extract of *N. sativa* seeds studied in mice and compared with sulfoxide-treated control mice was found to increase life span by 153%. Cancer-inducing agent dimethylbenzanthracene and croton oil are used to induce cancer in the skin of animal mice and had shown anti-cancer effects of *N. sativa* and *C. sativa* extract by topical application of it. Stomach carcinogenesis induced by benzo(*a*)pyrene in mice, in vivo, and in vitro inhibitory effect of TQ against had been shown (Salomi et al. 1991; Worthen et al. 1998).

5.8.5 Anti-diabetic Activity

A mixture with composition of *N. sativa*, myrrh, gum, asafetida, and aloe studied for its anti-diabetic effects in rats has shown lowering of glucose level; further it confirmed that hepatic gluconeogenesis is inhibited by this mixture. This mixture is used for the treatment of diabetes mellitus (Al-Awadi and Gumaa 1987; Al-Awadi et al. 1991). Alloxan an organic compound selectively destroys insulin-producing cells in pancreas-induced diabetes in rabbits; a notable hypoglycemic effect was found in animals further treated with *N. sativa* volatile oil (Al-Hader et al. 1993). It also confirmed seed extract of *N. sativa* given orally in alloxan-induced diabetic rabbits to cure the disease. Diabetes induced by drugs streptozotocin plus nicotinamide in hamsters and examines the insulinotropic properties of *N. sativa.* For the result after 4 weeks of treatment, glucose level decrease in blood along with high serum albumin level was observed (Fararh et al. 2002). Protective effects in diabetes were found when n-hexane and extract of *N. sativa* were used. A clinically studied design on 60 diabetic patients of *N. sativa* has shown to result in an improvement concerning total cholesterol and low-density lipoprotein cholesterol (LDL-C) (Najmi et al. 2008). Examining the effects of *N. sativa* seed oil and thymoquinone in streptozotocin-induced diabetes in rats, results revealed a significant increased concentration of norepinephrine and dopamine and simultaneous decrease in serotonin compared to the control group.

5.8.6 Antimicrobial Activity

A phenolic fraction of *N. sativa* had shown antibacterial effects; it was first confirmed by Toppozada et al. (Toppozada and Mazloum 1965). Several types of the research reported this plant has a broad range of antimicrobial activity. An in vitro study confirmed the inhibition of growth against microorganisms like *E. coli*, *Staphylococcus albus*, *Salmonella typhi*, *and Vibrio cholera* even with the dilution used is at a ratio 1:1000. Plate diffusion method had shown a result of inhibition against Gram-positive and Gram-negative bacteria. Examples of Gram-positive bacteria are *Bacillus subtilis* and *Staphylococcus aureus* and Gram-negative *E. coli* and *Pseudomonas aeruginosa*. Also, the growth of *Aspergillus* species is inhibited by using oil of seeds. A study found a significant decreased viral load in the liver and spleen when using murine cytomegalovirus as a model by intraperitoneal administration of oil (Salem and Hossain 2000).

5.8.7 Antiparasitic Activity

Several scientists have reported the anti-parasitic activity of *N. sativa* seed oil which had shown anticestodal and antinematodal effects and also found *Schistosoma mansoni* worms in the liver and the total number of ova present in liver and intestine organ (Mahmoud et al. 2002), (Shenawy et al. 2008). Another study reported that it

was effective against *Hymenolepis nana* helminths (Ayaz et al. 2007) and also effective against *Trichinella spiralis* and *Aspiculuris* worms (Abu El Ezz 2005).

5.8.8 Antimalarial

N. sativa extract exhibits anti-malarial activity reported by scientists and was experimented and found to have both in vivo and in vitro anti-plasmodial activity. Growth of *Plasmodium falciparum* inhibited against the strength of 50 μg/mL extracts; a dose-dependent effect had shown against the parasite.

5.8.9 Analgesic and Anti-inflammatory Activity

Houghton et al. (1995) studied the crude fixed oil and thymoquinone (TQ) of *N. sativa* in rat peritoneal leukocytes and revealed that in the metabolism pathway of arachidonate, the enzymes cyclooxygenase and 5-lipooxygenase were inhibited. Prevent the formation of thromboxane B2 and leukotrienes B4 and its dose-dependent effects observed. Further, these studies reported on the aqueous suspension of crushed seeds in animals (Al-Ghamdi 2001). Anti-inflammatory effects shown in the rat have taken aspirin drug as a standard and inhibit the formation of edema in rat hind paw using *N. sativa* (Khanna et al. 1993). Studies were performed using animal rats and mice; result of three tests for anti-nociceptive activity like hot plate test, tail pinched test, and the acetic acid-induced writhing revealed that the fixed oil of the seeds has strong anti-nociceptive effects because of an opioid substance in the oil which was antagonized by naloxone. The overall mechanism of both anti-inflammatory and analgesic is related to the prevention of eicosanoid synthesis (Houghton et al. 1995).

5.8.10 Anti-nociceptive Effects

Oil of Egyptian *N. sativa* was used for the study of anti-nociceptive effects in animals, and it was found nociceptive responses induced by thermal, mechanical, and chemical stimuli had suppressed. The anti-nociceptive effect of the extract is mainly because of the component thymoquinone and revealed at least the supraspinal opioid system (Abdel-Fattah et al. 2000a, b).

5.8.11 Anti-ulcer Activity

Akhtar et al. (1996) reported in his study that the ulcer produced by aspirin reduced by about 36% using aqueous extract of *N. sativa* seeds. Also, another study of *N. sativa* seed oil shows a protective effect on the stress gastritis in hypo-thyroidal

rats (Abdel-Sater 2009). Ulcer produced by *Helicobacter pylori* would be removed by the seed oil of *N. sativa* (Salem et al. 2010).

5.8.12 Anti-histaminic Action

Induced bronchospasm in guinea pigs by histamine and investigate the antihistaminic effects of TQ and its carbonyl fraction of *N. sativa* that cure the bronchospasm. It was the first investigated antihistamine effect (El-Dakhakhny et al. 2000). Nigellone is a substance found in *N. sativa*; its effects were found to inhibit the secretion of histamine from a mast in the body; it was demonstrated in an in vitro study. Possibly the mechanism behind it is a decline in the level of calcium and inhibition of the protein kinase C (Chakravarty 1993). Stings of scorpion and spider, dog, cat, and snake bites can be cured by a folk medicine of *N. sativa.* Possibly, the analgesic and anti-inflammatory effects of *N. sativa* are helpful for the treatment (Al-Jishi and Abuo 2003).

5.8.13 Effect on the Cardiovascular System

A positive effect had been shown in the treatment of hypertension when *N. sativa* along with honey or garlic was used. In anesthetized rats the pharmacological action of *N. sativa* volatile oil and its active component TQ on arterial blood pressure and hearts was investigated. The result of the experiment indicates that the decline in arterial blood pressure and heart rates is dose-dependent (Tahir and Ashour 1993). The drugs atropine, cyproheptadine, and hexamethonium antagonized the effects. 5-Hydroxytryptaminergic and muscarinic receptors are found in CNS; both receptors are involved in antagonism effects. In rats experimented, an oral dose of 0.6 mL/kg/day of *N. sativa* extract had shown a significant hypotensive effect for the treatment of hypertension, and this result can be compared with standard antihypertensive drugs nifedipine (Zaoui et al. 2002). The diuretic drug furosemide has doses of 0.5 mg/kg/day used to compare the diuretic effects of the extract that developed to reduce hypertension.

5.8.14 Cardioprotective Effect Against Hyperhomocysteinemia (HHcy)

Disease conditions of HHcy have several risks like coronary, peripheral, and cerebral artery disease. All disease is because of the induction of the pathogenic state of oxidative stress; animal experiments (rats) revealed a remarkable higher level of triglycerides, lipid peroxidation, and cholesterol. The activities of enzymes glutathione peroxidase and superoxide dismutase have notably declined because of antioxidant effects. Advantage of *N. sativa* either seeds or its purified constituents is that it has cytoprotective and antioxidant actions (Ali and Blunden 2003).

5.8.15 Anti-hyperlipidemic Effects

Scientists have reported much data based on animal models for lipid-lowering activity, where an orally administered extract of seeds had shown a prominent effect. Cholesterol and lipoprotein level decreases (El-Dakhakhny et al. 2000; Anwar and Tayyab 2007; Pourghassem-Gargari et al. 2009; Al-Naqeep et al. 2011). Lowering of total cholesterol, triglycerides, and LDL-cholesterol in humans was found when the powder of seeds is taken before breakfast (Bhatti et al. 2009; Datau et al. 2010).

5.8.16 Effect on the Gastrointestinal Tract

N. sativa was used as a digestive, carminative, laxative, and anti-jaundice for stomachache in Unani medicine from very ancient times (Chopra et al. 1956). Also, flatulence by regular use of oral *N. sativa* powder is reported. Experiment on guinea pig intestine had shown the antagonizing effects of nigellone the active principle of *N. sativa* when contraction is induced by histamine. Oil of *N. sativa* and its active substance thymoquinone, thymohydroquinone, and dithymoquinone had shown a choleretic effect; it influences the secretion of gastric and ethanol-induced ulcer in rats.

A study reported remarkably higher content of glutathione, as well as lower content of mucosal histamine and ulcer formation, and reported a protection ratio of 53.56% found in *N. sativa* oil. In a study, it has been reported the crude extract of *N. sativa* had shown a relaxation of spontaneous contraction of rabbit jejunum when a dose of 0.1–3.0 mg/mL was used. Inhibition of K+ induced contraction in a similar dose range (Gilani et al. 2019). The research report on hypothyroidism-induced development of acute cold restraint stress gastritis in rats had shown the protective effects of *N. sativa.*

5.8.17 Effect on the Respiratory System

Experimented on guinea pig to examine the effects of *N. sativa* seed's volatile oil, respiratory rate and intratracheal pressure enhance in a dose-dependent manner. The active substance thymoquinone of volatile oil was found only to increase the intratracheal pressure without significant effects on the respiratory rate. In asthma, the disease used volatile oil without thymoquinone as a potential respiratory stimulant (Tahir and Ashour 1993). The pharmacological activity of petroleum ether extract is 10 times more than those of crude extract of *N. sativa*. Nigellone isolated from the extract and in an in vitro study effectively inhibits the histamine release from the mast cells (Chakravarty 1993). To manage the wheeze that is associated with lower respiratory disease in children by using *N. sativa*, the effect of *N. sativa* is examined in patients of chemical war victims on respiratory symptoms (Boskabady and Farhadi 2008).

5.8.18 Effect on the Nervous System

Opioid receptors active for the narcotic analgesic activity when used with *N. sativa* seed oil had shown depressant effects on CNS and potential analgesic effect and enhance pentobarbitone-induced sleeping time (Khanna et al. 1993). More activity of GABA has been found, while secretions of the following glutamate, aspirate, and glycine decrease. All pharmacological changes indicate the sedative and depressive effect of seed extract of *N. sativa* (El-Naggar et al. 2010). Scientists reported multiple times administrations of *N. sativa* also decline the production of 5 HT and had shown anxiolytic effects. An experiment was conducted on mice and had shown the anticonvulsant effect of thymoquinone that is the major constituent of *N. sativa* seeds (Hosseinzadeh and Parvardeh 2004, Hosseinzadeh et al. 2005).

5.8.19 Effect on the Immune System

Since ancient times, folk medicine has been practicing to use *N. sativa* seeds and also oil of the seeds which promote good health. In in vitro studies, it has been found that on the immune system, the effect of *N. sativa* is to enhance the immune properties in human T-cells. Seeds of *N. sativa* activate T-lymphocyte to release the interleukin, IL-3, and IL-1B production (Haq et al. 1995). Purified protein molecules of seeds had shown some suppressive and other stimulatory properties in lymphocyte culture.

5.8.20 Effect on the Genitourinary System

Experimented on guinea pig and rats is the inhibitory effect of *N. sativa* oil on spontaneous concentration in uterine smooth muscle induced by oxytocin (Aqel and Shaheen 1996). *N. sativa* crude oil had shown the same effects in in vivo studies of pregnant rabbits and in vitro of non-pregnant rats (Elnourm and Abdelsalam 2018). Hexane solvated extract of *N. sativa* had shown mild uterotropic activity and prevented pregnancy in rats (Keshri et al. 1995) (Table 5.2).

5.8.21 Effect on the Reproductive System

N. sativa seed had shown effects on reproductive organs. A study that observe in 60 days the increase in the weight of reproductive organs, sperm motility, and count in cauda epididymidis and testicular ducts. Primary and secondary spermatocyte, increased spermatogenesis was found. In female pregnant rats, fertility increases (Mukhallad et al. 2009; Al-Sa'aidi et al. 2009).

Table 5.2 Selected studies showing the different doses and routes of administration of *N. sativa* seed grains and extracts tested in experimental models in vivo

S. no.	Animal	Model	Route	Dose	Reference
1	Chicks	Toxicity	Diet	Grains 20, 200 g/kg	Al-Homidan et al. (2002)
2	Rats	Methylnitrosurea-induced colon cancer	Oral	0.2 g/day	Mabrouk et al. (2002)
3	Mice	Candidiasis infection	Oral	Extract 6.6 mL/kg	Khan et al. (2003a)
4	Rats	KBro3-induced toxicity	Oral	50 mg/kg	Khan et al. (2003a)
5	Mice	Skin carcinogenesis	Topical	100 mg/kg	Salomi et al. (1991)
6	Mice	Ehrlich ascites carcinoma	Oral	100 mg/kg	Salomi et al. (1992)
7	Mice	Carrageenan-induced edema	Oral	500 mg/kg	Al-Ghamdi (2001)
8	Mice	Nociceptive activities	i.p.	100 mg/kg	Al-Naggar et al. (2003)
9	Mice	MCMV (virus) infection	i.p.	2 mg/kg	Salem and Hossain (2000)
10	Rats	Colon carcinoma	Oral	200 mg/kg	Salim and Fukushima (2003)
11	Rats	Gentamicin-induced toxicity	Oral	0.5–2 ml/kg	Ali (2004)
12	Mice	Schistosoma mansoni infection	Oral	2.5, 5 mg/kg	Mahmoud et al. (2002)
13	Rats	Homeostasis	Diet	180 mg/kg	Al-Jishi and Abuo Hozaifa (2003)
14	Rats	Cisplatin-induced toxicity	i.p.	50 mg/kg	
15	Guinea pigs	Urethane anaesthetization-induced respiratory pressure	i.v.	4–32 μL/kg	Tahir and Ashour (1993)
16	Rats	Ischemia-/reperfusion-induced gastric lesion	Oral	2.5, 5 mL/kg	El-Abhar et al. (2003)
17	Rats	CCl_4-induced toxicity	Oral	800 mg/kg	El-Abhar et al. (2003)
18	Mice	STZ-induced diabetes	i.p.	400 mg/kg	
19	Rats	Carrageenan-induced edema	Oral	100,400 Al/kg	Hajhashemi et al. (2004)
20	Rats	Croton oil-induced ear edema			
21	Mice	Typhoid immunization/Abs	Oral	0.2 mL/kg	Islam et al. (2004)
22	Rats	STZ-induced diabetes	i.p.	0.2 mL/kg	Kanter et al. (2004)
23	Rats	CCl4-induced toxicity	i.p.	0.2 mL/kg	Kanter et al. (2003)
24	Rats	Anti-fertility against pregnancy	Oral	2 g/kg	Keshri et al. (1995)

(continued)

Table 5.2 (continued)

S. no.	Animal	Model	Route	Dose	Reference
25	Mice	Nociceptive-induced insults	Oral	50,400 mg/kg	Abdel-Fattah et al. 2000a, b)
26	Rats	Methionine-induced HHcy	Oral	100 mg/kg	El-Saleh et al. (2004)
27	Rats	Blood homeostasis	Oral	1 mg/kg	Zaoui et al. (2002)
28	Mice	Nociceptive-induced insults	Oral	2.5–10 mg/kg	Abdel-Fattah et al. 2000a, b)
29	Rats	Ifosfamide-induced FS	Oral	5 mg/kg	Badary et al. (1999)
30	Mice	Ehrlich ascites carcinoma	Oral	10 mg/kg	Badary et al. (1999)
31	Rats	DOX-induced toxicity	Oral	10 mg/kg	Badary et al. (2000)
32	Mice	Benzo(*a*)pyrene-induced stomach tumor	Oral	0.01%	Badary et al. (1999)
33	Mice	Methylcholanthrene-induced sarcoma	Oral	0.01%	Badary and Gamal El-Di (2001)
34	Rats	Arterial blood pressure	i.v	0.2 mg/kg	Tahir and Ashour (1993)
35	Guinea pigs	Urethane anaesthetization-induced respiratory pressure	Oral	1.6–6.4 mg/kg	Tahir and Ashour (1993)
36	Rats	Ischaemia-/reperfusion-induced gastric lesion	Oral	5–100 mg/kg kg	El-Mahmoudy et al. (2002)
37	Rats	Methionine-induced HHcy	Oral	100 mg/kg	El-Saleh et al. (2004)
38	Rats	Acetic acid-induced colitis	Oral	5–10 mg/kg	Mahgoub (2003)
39	Mice	CCl4-induced toxicity	i.p.	4–50 mg/kg	Mansour et al. (2001)
40	Mice	Determination of LD50 = 90 mg/kg	i.p.	78–103 mg/kg	Mansour and Tornhamre (2004)
41	Mice	Inflammation (EAE model)	i.v.	1 mg/kg	Mohamed et al. (2003)
42	Rats	CCl4-induced toxicity	Oral	100 mg/kg	Nagi et al. (1999)
43	Rats	DOX-induced toxicity	Oral	10 mg/kg	Nagi and Mansour (2000)

5.8.22 Effect on Blood

An experiment was performed in male rabbits and reported that the petroleum ether extract of *N. sativa* indicated its action on blood coagulation and was found to lessen the time of blood clotting, plasma clot, and kaolin cephalin clot when compared with control. Further in a study on rats, a shortening of bleeding time was confirmed (Bamosa et al. 2010).

5.9 Toxicological Report

A low level of toxicity was indicated in seed extract and its component also. Studied toxicity of fixed oil (10 mL/kg for 12 weeks) of seeds in mice and rats reported LD50 values, and the possible biochemical, hematological, and histopathological changes were investigated. Information such as LD50 values 11.915 mL/kg, key hepatic enzyme stability, and organ integrity values came from the research study and indicates that a therapeutic dose of fixed oil is safe. Thymoquinone LD50 value was reported at 2.4 g/kg. A remarkable decline in glucose concentration observed in mice when used 90 days has 0.03% concentration of thymoquinone in drinking water, but no signs of toxicity (Zaoui et al. 2002).

Induced toxicity in rats by diazinon drug. Toxicity is induced in organs such as hepatotoxicity, immunotoxicity, hepatotoxicity, nephrotoxicity, and cardiotoxicity in rats. These animals were treated with seed extract of *N. sativa* with duration of 3–6 weeks orally. Founded, thymoquinone as a therapeutic agent against the organ toxicity. Hematological disorder induced by aflatoxin and cadmium can be cured with the treatment of a standard dose of *N. sativa* (Abdel-Wahhab and Aly 2005; Demir et al. 2006). For bone marrow toxicity induced by carbon tetrachloride in animals, treated with *N. sativa*, no remarkable pathological changes were recorded (Abou Gabal et al. 2007).

5.10 Therapeutic Enhancement of Thymoquinone in Nanoformulation

With bioactive compounds solubility is a very big problem for the development of formulation, its effects, and the therapeutic value. Compounds if the nature is lipophilic have a limitation in the development of formulation also. Thymoquinone is one of the most important substances found in *N. sativa*, and it has numerous therapeutic effects. In conventional formulation bioavailability of the compound is a major problem; it can be overcome by developing a nanoformulation, which enhances the therapeutic effects. Nanoformulation of thymoquinone against several diseases (Table 5.3).

5.11 Conclusion and Future Perspectives

N. sativa has several substances and shown a number of therapeutic potential against various diseases like diabetes, neuropathic pain, ulcerative colitis, cancer, heart disease, CNS disorder, musculoskeletal disease, and other diseases also. One of the important substances TQ is found in the plant which shows several pharmacological properties. The study reported a favorable pharmacokinetic, low toxicity that makes it safe. A high therapeutic index and safety data make TQ a good candidate for drug development. Since ancient times the edible plants are considered safe particularly in Middle East countries; the TQ substance presence makes it very

Table 5.3 Important nanoformulation of thymoquinone against several diseases

S. no.	Nanoformulation	Facts	References
1	Three piperine, sulforaphane, and thymoquinone nanoformulation	Bioactive phytochemical nanoformulation developed for the treatment of breast cancer, enhance their bioavailability by targeted delivery system with reduce systemic dose	Aumeeruddy and Mahomoodally (2019)
2	Thymoquinone nanoformulation	Delivery of the bioactive compound thymoquinone loaded in PLGA-chitosan nanoparticles in the brain through intranasal pathways, enhanced their pharmacokinetic profile. Used the formulation for the neuroprotection and treatment of cerebral ischemia	Xiao et al. (2016)
3	Thymoquinone nanoformulation	Antihyperglycemic effects of thymoquinone-loaded NCs (containing 10, 20, and 40 mg of thymoquinone) compared with thymoquinone and metformin. Produced better effects half dose of thymoquinone in type 2 diabetic rats	Rani et al. (2018)
4	Thymoquinone nanoformulations: nanonutraceuticals	Nano-TQ effectively augments the anticancer roles of doxorubicin by upregulation of P53 and downregulation of Bcl2 and potentiates paclitaxel's apoptosis in MCF-7 breast cancer cells	El-Far et al. (2018)
5	Streptozotocin + nicotinamide-induced diabetic rats through combinational polymeric nanoformulation	The bioactive compounds glycyrrhizin (GL) and thymoquinone (TQ) have been reported for antidiabetic activity in pure and nanoformulation (NF) form. Administration of combined GT NFs exhibited significant improvement in studied parameters. Improvements in antidiabetic activity could have been due to a synergistic effect of combined NFs, leading to enhanced absorption of NFs and lesser cytotoxic effects compared to pure bioactive compounds	Rani et al. (2019)
6	Loading of doxorubicin and thymoquinone with F2 gel nanofibers	Nanoformulation of doxorubicin (DOX) and thymoquinone (TQ) loaded with nanofibers of poly-N-acetyl glucosamine	Zidan et al. (2018)

(continued)

Table 5.3 (continued)

		(pGlcNAc), which is known as F2 gel, over their conventional free forms. Nanoformulation showed dramatic increase in apoptosis, caspase 3, and antioxidant enzymes; in contrast to dramatic fall in cell viability, tumor volume, oxidative and nephrotoxicity markers, and NF-κB compared to corresponding free therapies	
7	Thymoquinone delivered by mesoporous silica core-shell nanoformulations	Novel core-shell nanoformulations for TQ delivery against glioma cells using mesoporous silica nanoparticles (MSNs) as a carrier. A high TQ release from MSNTQ was detected at neutral pH 7.4, while a high TQ release from MSNTQ-WA and MSNTQ-CS was obtained at acidic pH 5.5 and 6.8, respectively; thus, TQ release in acidic tumor environment was enhanced	Shahein et al. (2019)
8	Thymoquinone-loaded solid lipid nanoparticles	Treatment with 10 and 20 mg/kg b.w of thymoquinone-loaded solid lipid nanoparticles (TQ-SLNs) and 80 mg/kg b.w of thymoquinone suspension (TQ-S) showed a significant ($P < 0.01$) improvement in ATPases function in 3-NP-induced animals than TQ-S (40 mg/kg b.w)-treated group. TQ-SLNs (10 and 20 mg/kg) treatment also attenuated the overexpression of glial fibrillary acidic protein (GFAP), pro-inflammatory cytokines, and p-p65 NFκB nuclear translocation in 3-NP-exposed animals	Ramachandran and Thangarajan (2018)
9	PLGA-PEG thymoquinone nanoparticles	Two types of TQ-nanoformulation and its cytotoxicity toward resistant breast cancer cells. This study showed that nanoparticle synthesized with 1:7 drug to PLGA-PEG ratio and 2:1 PLGA-PEG to Pluronic F68 formed	

(continued)

Table 5.3 (continued)

		nanoparticles with less than 100 nm and had spherical shape as confirmed with DLS. This could facilitate its transportation and absorption to reach its target	
10	Thymoquinone-loaded PLGA nanoparticles	To formulate a nanoformulation (PLGA-NPs) and to improve brain bioavailability for thymoquinone (THQ) through intranasal (i.n.) drug delivery. Evaluation of pharmacokinetic parameters, biodistribution studies, brain drug-targeting potential (89.89 ± 9.38%), and brain-targeting efficiency (8075.00 ± 113.05%) studies through intranasal administration which showed an improved THQ brain bioavailability	Ahmad et al. (2020b, b)
11	Thymoquinone-loaded solid lipid nanoparticles	Anti-inflammatory and neuroprotective effects of TQ which may be associated with 5-HT pathway. Thus, the present study offers a newer approach to reduce symptoms of depression using thymoquinone solid lipid nanoparticle	Alam et al. (2020)
12	Thymoquinone niosomes	From thymoquinone noisome release of TQ studied, the release kinetics data showed Higuchi's equation with highest regression coefficient values. The permeation study and the confocal laser microscopy study further confirmed the enhancement in permeation of TMQ in the intestinal mucosa	Gilani et al. (2019)
13	Thymoquinone in liposomes	Thymoquinone (2-isopropyl-5-methyl-1,4-benzoquinone) is a herbal-derived drug with potential chemopreventive and chemotherapeutic activity. The TQ-LP liposomes were effective in suppressing the proliferation of breast cancer cell lines MCF-7 and T47D and at the same time exerting very low toxicity on normal periodontal ligament fibroblast	Odeh et al. (2012)

(continued)

Table 5.3 (continued)

14	Thymoquinone-loaded nanoproniosomal formulation	Thymoquinone proniosomal formulation (TQP) and evaluate their efficacy in methotrexate (Mtx)-induced hepatotoxicity in rats. The high entrapment efficiency is probably due to the lipophilic character of TQ. The release of TQ from developed formulation was found to be significantly higher compared to control	Sayeed et al. (2017)
15	Liposphere-mediated topical delivery of thymoquinone	Thymoquinone lipospheres of particle size below 70 nm were prepared and evaluated. These lipospheres resulted in deeper skin penetration, slow release, and skin compatibility. Anti-inflammatory and anti-psoriatic potential of lipospheres was determined using in vitro cell lines and imiquimod-induced psoriatic plaque model	Jain et al. (2017)

valuable for health. Daily intake prevents several diseases. Apart from the medicinal uses, it is used in food industries as an additive, flavoring agent, and preservative. Research studies suggest its use as a nutraceutical.

Further, research in humans and animal models is required to explore the mechanism of action of the active component particularly TQ and other active components of *N. sativa* seeds at a cellular and molecular level. Studies require exploring the mechanism of action of several therapeutic effects like anti-inflammatory, anti-cancer, etc. Chemical modifications in the molecular structure of TQ and other substances show more therapeutic effects and are required to investigate the mechanism of such effects by performing animal studies. In the future, it becomes more effective for the treatment of various diseases. Further focus on preclinical and clinical studies on the use of *N. sativa* for the treatment of different diseases is needed (Ahmad et al. 2013; Goyal et al. 2017).

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A Review on Ethnomedicinal, Phytochemistry and Pharmacological Activities of *Rumex hastatus* D. Don

6

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Abstract

This book chapter summarizes selected scientific evidence on phytochemistry and pharmacological potential of *Rumex hastatus*. This herb is a bushy shrub and is an annual, biennial and perennial herb. The edible parts of the plant are young leaves and shoots (Padulosi 1999) belonging to the family Polygonaceae, and it is commonly known as *khatima*l. *R. hastatus* is commonly found in northern Pakistan, southwest of China and northeast Afghanistan. In India, it is widely distributed in western Himalayas, Himachal Pradesh, Jammu and Kashmir and Uttaranchal. It has been reported to possess a wide range of traditional medicinal uses including in asthma, cancer, rheumatism, diuretic, diarrhoea, dysentery, toothache, gum healing, jaundice, hepatitis, cough, fever, piles, carminative, purgative, fungal infection, lungs, bleeding and as a flavouring agent. Preliminary phytochemical screening showed that this plant is rich in various chemical constituents which are medicinally important such as flavonoids, anthraquinones, cardiac glycosides, alkaloids, terpenoids, tannins, saponins, phenolic compounds and coumarins. It has anti-nociceptive, antipyretic, anti-inflammatory, hepatic protective, anticholinesterase, antioxidant, antiradical, cytotoxic, anti-tumour, and angiogenic potential. The objective of the present current chapter is to collect all the relevant research articles which give information regarding traditional uses, phytochemistry and therapeutic potential of *R. hastatus. R. hastatus* has potential for curing various diseases and has been well studied for its phytochemical properties. However, further scientific studies are needed to explore mechanisms of actions, adverse effects of the extracts, toxicity and the therapeutic effect of major secondary metabolites.

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Keywords

Rumex hastatus · Therapeutic potential · Phytochemical properties · Polygonaceae

Abbreviations

A. flavus	*Aspergillus flavus*
A. fumigatus	*Aspergillus fumigatus*
A. niger	*Aspergillus Niger*
ABTS	2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
AChE	Acetyl cholinesterase
AD	Alzheimer's disease
AIDS	Autoimmuno deficiency disease
BChE	Butyrylcholinesterase
ca.	Circa (approx.)
CAM	Chorioallantoic membrane assay
Cox-2	Cyclooxygenase-2
DNA	Deoxyribonucleic acid
DPPH	Diphenyl-1-picrylhydrazyl
E. coli	Escherichia coli
EtOH	Ethanol
F. solani	*Fusarium solani*
FID-MS	Flame ionization detector with mass spectrometer
H_2O_2	Hydrogen peroxide
HDL	High-density lipoproteins
IUCN	International Union for Conservation Research
LC50	Lethal concentration
LDL	Low-density lipoproteins
MeOH	Methanol
NSAIDs	Non-steroidal anti-inflammatory drugs
PFAF	Plants for a future
PHCs	Primary health Centre
R. hastatus	*Rumex hastatus*
STD	Sexually transmitted disease
TC	Total cholesterol
TLC	Thin layer chromatography
TNF	Tumour necrosis factor
Tsp	Teaspoon
UPLC-DAD	Ultra-performance liquid chromatography method with diode array detection

6.1 Introduction

An examination is required to characterize and portray the future errands of phytochemical research in the new millennium and not just of the present status of improvement of phytochemical research yet in addition to chemosynthetic pharmaceutical exploration. Both end up in a race to grow new prescriptions, with less or no reactions, for restorative and preventive application in illnesses for which casualty-based treatment has been nonexistent or blemished (Yaniv and Bachrach 2005). Use of plants as drugs has started between 4500–1600 BC and 2500–600 BC in Rig-Veda and Ayurveda, respectively. Apart from this, they have been used by Greeks and Arabs in the history, which saw its rise to India and Europe as well (Jan et al. 2011). Different plant species are developed and utilized as vegetables and food, throughout the globe; however huge numbers of these are ignored and underutilized. These are labelled "dismissed or underutilized" on the grounds that they remain ineffectively described and abandoned by examination and protection. Likewise, they have been maintained by social tendencies and conventional framework. Continuous negligence of these vegetables implies that their potential centrality will be underestimated, henceforth underestimated at this point, yet a large number of them are light and versatile and bear unfavourable climatic conditions more than the fascinating ones. Extraordinary danger of delayed hereditary eroding and vanishing is put on them, which could additionally prevent opportunity choices for the country occupants (Padulosi et al. 1999; Johns and Eyzaguirre 2006; Mal 2007; Ghane et al. 2010). A portion of these disregarded and underutilized crop species might be wild, yet their jobs are indispensable in food security and nourishment and financially assist the people living below the poverty line in the provincial territories of the emergent nations (Magbagbeola et al. 2010). Vital medicinally important constituents are present in herbs producing distinct physiological activity on the human body. Alkaloids, tannins, flavonoids, terpenoids, saponins and phenols include the significant ones. Due to their therapeutic significance and low poisonousness, drug specialists are concerned about their exploration (Inayatullah et al. 2012). Isolation of many such entities has been established from different plants with perhaps novel mechanism of actions and negligible poisonousness to the host cell (Ahmad and Aqil 2007).

6.1.1 *Rumex* and Polygonaceae

Ever since the time humans use plants and spices as cure against maladies and infirmities because of their healing benefits and different restorative focal points, *Rumex* L. (Dock) species have increased gigantic acknowledgement (Babulka 2004). Two huge clades were characterized after the atomic phylogenetic investigation by Navajas-Pérez et al. (2005) inside the variety *Rumex*, one framed by the species of subg. *Rumex* and the other made out of the species of subgenera Acetosa (includes

Rumex hastatus), acetosella and platypodium. Various *Rumex* species have been customarily utilized in various places of the world which in history have verifiable foundation. Propensities to utilize plants for various purposes, for example, medication, food, pharmaceuticals and so forth, are inculcated on the basis of interrelationship among the past, the present and what's to come, which is woven in human civilizations (Zhang et al. 2014). The two spheres of well-being which include ethnoveterinary and ethnomedicine are the main aspects in clinical practice where the plants have a great utility (Abbasi et al. 2013; Disler et al. 2014; Bartha et al. 2015; Hussain et al. 2015; Vogl et al. 2016). In the family Polygonaceae, *Rumex* is the second largest genus. It is widely distributed in most part of Europe, North America, Africa and Asia, predominantly in the northern half of the globe (Vasas et al. 2015). The family Polygonaceae generally known as the knotwood or smart weed family is a group of blooming or flowering plants (Uddin et al. 2014) and involves 56 plant genera with 5109 logical plant names of species, of these 1266 are acknowledged species names. A further of 1675 scientific plant names of intraspecific position for the family Polygonaceae are incorporated in the plant list (List 2010), among which *Eriogonum* (2410 species), *Rumex* (200 species), *Coccoloba* (120 species) and *Persicaria* (100 species) are the biggest ones (Uddin et al. 2014). Numerous types of this class are herbs; however some are bushes as well, and a couple are rhizomes. The genus *Rumex* is a commonly recognized name, represented by 25 perennial plant species in nations like Poland. In traditional medicine leaf, seeds, fresh plant juice, seeds, and aerial parts are the generally utilized. Rich hereditary diversity in a few wild plants of nutritional worth and potential therapeutic properties is mostly found in the West Himalayan biogeographic zone, which is known for it (Sinha and Sinha 2001; Singh et al. 2002). Asthma, bronchitis, cough, loose bowels, diarrhoea, dermatitis, ear infection, inflammatory conditions, jaundice, kidney disease, leprosy, toothache, ulcerative colitis and intestinal parasites are among the few medicinal properties credited to this family (Uddin et al. 2014).

6.1.2 *Rumex hastatus* D. Don

R. hastatus belongs to the family Polygonaceae and is commonly called as "Khatimal". It is found in abundance in northern Pakistan, southwest China and northeast Afghanistan (Shinwari and Gilani 2003). The leaves and shoots are used in chutneys and pickles due to its pleasant acidic taste (Manan et al. 2007). It is reported that the whole plant is used as medicine. It is laxative, alterative and tonic (Shinwari and Gilani 2003) and used for treating sexually transmitted diseases like AIDS (Sahreen et al. 2011). The aqueous extract of the roots of *Rumex* is used traditionally for curing asthma (Abbasi et al. 2010, Abbasi et al. 2011). The leaves and young shoots are used as carminative, purgative, diuretic and in stomach problems (Murad et al. 2011). All the previous studies on *R. hastatus* leaves have proven them to be constituting righteous phenolic principles and are therefore verified antioxidant

sources. (Zhang et al. 2009; Sahreen et al. 2011) reported seven phenolic compounds from *R. hastatus* roots by referring the use in Chinese herbal system. The *R. hastatus* has been evaluated for various activities like antioxidant (Sahreen et al. 2011); antifungal (Hussain et al. 2010); antifungal and anti-bacterial (Hussain et al. 2010); antidiarrhoeal (Shakuntala et al. 2011) and anti-viral (Taylor et al. 1996).

6.1.3 Review Methodology

There is no literature of review on *R. hast*atus that has been published yet; therefore the book chapter on the present topic was assembled with the goal of compiling the relevant data on the plant till date, this species being sparsely explored as compared to its other allies and species. The collection of selection of relevant data was made through a search using the keyword "*Rumex*," "*R. hastatus*". Pertinent data was collected from various major scientific databases including Medline, Scopus, ScienceDirect, Prota, SciFinder, PubMed, Google and Google Scholar, and plant taxonomy was validated by the databases *Mansfeld's Encyclopedia*, *The Plant List*, and PFAF. Various publication sites like Taylor and Francis, Elsevier and Springer used to collect the literature. Additional information on traditional use and botany was obtained from published books and MSc dissertation. A total of about 250 papers and articles were compiled which were published in different journals until May 2020. Data was analysed from different perspectives. All the literature was searched with the aim of obtaining data from different parts of the world and not specifically a particular region, thereby covering a vast and imperative field of knowledge. This was done to obtain the necessary data and research on the pertaining topic, until the present time. On the basis of 161 references, the present review was designed to provide a survey of the current state of knowledge of the phytochemistry and isolation; morphology and anatomy; nutritional importance; ethnobotany; and pharmacological activities of *R. hastatus*, as well as its traditional uses which have been supported by pharmacological investigations in order to identify its relevance as food and potential therapeutic applications and to show further directions of research (Table 6.1).

6.2 Ethnobotany

R. hastatus is quite rampant across the globe, and it is known by a variety of names in different languages.

Synonyms

Rumex arifolius (List 2013)

Rumex dissectus (Abbasi et al. 2011)

Taxonomical Classification

Kingdom	Plantae
Subkingdom	Angiosperms
Division	Flowering plants
Class	Magnoliopsida
Subclass	Caryophyllidae
Order	Caryophyllales
Family	Polygonaceae
Genus	*Rumex* L.
Species	*Hastatus* D. Don

Conservation Status.
R. hastatus is included in IUCN Red List of threatened plants.

6.2.1 Habitat and Edible Part

Being a bushy shrub, *R. hastatus* is about 30–90 cm high (Singh et al. 2013a, b). The young shoots and leaves of this plant are edible (Sher et al. 2015; Seidemann 2005).

6.2.2 Ecology

6.2.2.1 Altitude

R. hastatus D. Don is mainly distributed at elevations of about 2400 m (Dutt et al. 2015). In Nepal, it however occurs at an elevation of 1000–2600 m (Manandhar 2002).

Table 6.1 Showing the different names of *Rumex hastatus* across the region

Country	Language	Name	References
India	Hindi	Kattameetha and almoru	Singh et al. (2014), Bisht and Sharma (2014)
India	Hindi	Khatapalak	Seidemann (2005),
India	Hindi	Churki, Bhilmora	Verma (2019), Dutt et al. (2015), Shedayi et al. (2014)
India	Hindi	Ammi, Khattiambi	Bhatia et al. (2018), Kumari et al. (2013)
India	Kumauni	Amlora, Chulmora	Verma (2019)
Pakistan	Hindko	Khitml	Abbasi et al. (2011)
Pakistan	Punjabi	Khattimal, Katamba	Verma (2019)
Pakistan	Urdu	KhattiButi	Verma (2019), Sher et al. (2015), Ullah et al. (2014)
Pakistan	Pashto	Tarukay	
Pakistan	Pashto	Teerwoki	Ullah et al. (2010)
Pakistan	Khowar	Sirkunzo	Ullah et al. (2014)
Nepal	Nepali	Kapu, Charimaal	Verma (2019)
Germany	German	Spiebigger, Ampfer	Seidemann (2005)
Europe	English	Arrowleaf dock, yellow sock, curled sock	Verma (2019)

6.2.2.2 Climate, Soil, pH and Lifespan

R. hastatus can grow in semi-shade (light woodland) or no shade. It can grow in wasteland, dry slopes and rocks (Dutt et al. 2015), shady slopes or dry streambeds (Manandhar 2002). The soil which is suitable for its growth includes light (sandy), medium (loamy) and heavy (clayey) soils and preferably well-drained soil. *R. hastatus* is an annual, biennial and perennial herb belonging to the family Polygonaceae. The common perennial herbs which grow in sour and acidic soils are members of this family (Zabta et al. 2003).

6.2.3 Distribution

R. hastatus is widely distributed in northeast Afghanistan, in north of Pakistan and southwest of China at an altitude of 700–2500 m (Qaiser 2001). In India the *Rumex* is widely distributed in Kumaun, Himachal Pradesh, Uttarakhand, Chandigarh, western Himalayas and Jammu and Kashmir (Zabta et al. 2003; Seidemann 2005; Paul and Chowdhury 2019). In Himachal Pradesh, the plant is found in Hamirpur, Lahual Chamba, Kullu and Spiti (Singh et al. 2014). It is also found in Mongolia, Russia, Tajikistan,Kazakhstan, Kyrgyzstan, Europe (Paul and Chowdhury 2019), Muree and Gilgit/Baltistan (Hameed et al. 2010).

6.2.4 Phenology

Flowering time: May–June (Hameed et al. 2010).

Fruiting time: March–November (Singh et al. 2014).

6.2.5 Pollination

R. hastatus is a hermaphrodite (has both male and female organs), and it is mostly pollinated by wind.

6.2.6 Propagation

R. hastatus is propagated through seeds, which can be sown in spring. The seedlings are transferred in pots individually when they are large enough to handle and planted out in the summer. Division takes place in spring.

6.2.7 Morphology and Description

Stem: The stem is herbaceous above and woody below and is erect and branched (Abbasi et al. 2011). The branches are finely grooved, purple-brown; branchlets are green and glabrous and about 50–90 cm tall (Anjen et al. 2003).

Leaves: The colour of the leaves is pale green with simple lobes which are directed outwards (Abbasi et al. 2011). The central lobe is narrowly triangular and linear. Leaves are solitary or fascicled; the blade is 1.5–3 cm × 1.5–2 mm and the petiole is 1.5–3.5 cm; apex is acute; basal lobes are curved; pedicel is slender and articulate below the middle; ocrea is fugacious and membranous (Anjen et al. 2003).

Roots: The roots are cylindrical, 0.5–0.9 cm wide and 3.5–6.5 cm long. The roots have transverse fissures and dark brown colour on upper surface. The inner surface is brown in colour and the fracture is short and mealy (Singh et al. 2013a, b).

Flowers: The flowers are numerous, small, pinkish in terminal paniculate clusters (Abbasi et al. 2011). They are polygamous. The petals of the male flowers are nearly uniform. In the female flowers, however, the outer petals are elliptic, and the inner ones are enlarged in fruit. Achenes are brown, ovoid, trigonous and shiny, ca. 2 mm. The valves are membranous, pinkish, orbicular or reniform, nearly pellucid, with small tubercle at the base; base is deeply cordate, apex is obtuse, and the margin is nearly entire (Anjen et al. 2003).

Fruits: *R. hastatus* bears one-seeded nutlet and fruit is pinkish (Abbasi et al. 2011).

6.3 Ethnomedicinal Importance

Traditional folk medical practices are empirical in nature; several million people with limited access to organized modern health-care centres depend on traditional systems of medicine to cater their primary health-care needs. Traditional systems of medicine are widely acknowledged to be effective and safe without any side effects (Farnsworth 1988). It has been ethnomedicinally used for various ailments. Various parts of the *R. hastatus* like leaves, roots, and stem are used in therapy. Different forms of preparation of this medicinal plant are employed (Table 6.2).

6.4 Nutritional Importance

In outlining the nutritional facts, the food quality and figures should be one of the major areas. *R. hastatus* is notable for its therapeutic importance; it is additionally utilized as nourishment for people. Leaves which are sour in taste are eaten raw as salad or made into chutney (Singh and Thakur 2014; Bhatia et al. 2018). To be concluded as a nutritional source and functional food, several authors assessed the nutritional and dietary properties of the plant and proved it as such (Ahmad et al. 2019). Many studies suggested that *R. hastatus* contains ample nutritional constituents and is a vital source of secondary metabolites, which can prove to be

Table 6.2 Traditional therapeutic uses for *Rumex hastatus*

Part used	Indication	Herbal preparation	Dosage form	References
Leaves	Toothache and gum healing	Dried powder	2 times a day	Rahman et al. (2016)
Stem, leaves, roots	Cancer	NAD[a]	NAD[a]	Alberto et al. (2016), Mishra et al. (2018)
Roots	Diarrhea and dysentery	Powder or paste or juice of root	2 tsp. 3 times a day (juice)	Coburn (1984), Pohle (1990), Manandhar (1995)
Roots and leaves	Wound healing in goats, cows and buffaloes	Powder	Given orally with flour for 4 days	Tariq et al. (2014)
Roots	Asthma	A sweet meal is made by mixing roots with *Quercus incana* and boiled with water. Sugar and semolina are added and cooked for 15 min	For children: 2–4 tsp., 2 times a day for 3–4 days. For adults: 8–10 tsp., 2–3 times a day, for 10–15 days	Abbasi et al. (2010)
Root	Rheumatism	Decoction	NAD[a]	Manandhar (2002), Abbasi et al. (2011), Shinwari and Gilani (2003)
Leaves and shoots	Diuretic	Leaves are directly eaten		Haq et al. (2011), Islam et al. (2006)
Roots, leaves	Jaundice and hepatitis	Root extract or fresh leaves are crushed along with water and sugar	One cup extract twice a day for 2 weeks	Haq et al. (2011), Singh and Thakur (2014), Singh and Attri (2014), Nadkarni and Nadkarni (1976)
Leaves	Appetizer	NAD[a]	NAD[a]	Sher et al. (2015)
Leaves	Blood purification	Leaves are directly eaten	NAD[a]	Ullah et al. (2010)
Root	Digestive ailments in cattle	Roots are taken and mixed with the powder of bark of *Quercus incana* and then boiled along with sugar and flour	Used for 10–15 days	Aziz et al. (2018)
Leaves	Blood pressure	Juice	NAD[a]	Singh and Thakur (2014)

(continued)

Table 6.2 (continued)

Part used	Indication	Herbal preparation	Dosage form	References
Whole plant	STDs including AIDS	NAD[a]	NAD[a]	Vermani and Garg (2002), Zhang et al. (2009)
Roots	Cough and fever	Decoction	NAD[a]	Abbasi et al. (2010)
Leaves and young shoots	Carminative and purgative	NAD[a]	NAD[a]	Murad et al. (2011)
Roots	Piles	NAD[a]	NAD[a]	Gorsi and Miraj (2002)
Tuber	Tonsillitis and sore throat	Juice	Tuber is directly chewed	Ullah et al. (2014), Manandhar (2002)
Leaves	Giddiness and insanity	NAD[a]	NAD[a]	Pande et al. (2007)
Root	Skin disease	NAD[a]	NAD[a]	Manandhar (2002)
Leaves and shoots	Refrigerant and cooling agent	NAD[a]	NAD[a]	Hussain et al. (2006), Ahmad (2007).
Roots	Antiseptic	Root extract	NAD[a]	Singh and Attri (2014)
Roots	Headache	NAD[a]	NAD[a]	Kuete et al. (2013), Vasas et al. (2015)
Roots	Lungs bleeding	NAD[a]	NAD[a]	Gorsi and Miraj (2002)
Roots	Backache	Decoction of roots	NAD[a]	Abbasi et al. (2010)
Leaves and young shoots	Flavouring agent	Powder	NAD[a]	Murad et al. (2011), Ullah and Rashid (2007)
Roots	Bone fracture	NAD[a]	Orally	Ijaz et al. (2016)
Leaves	Irritation by stinging nettles, scorpion sting, snake bite	Paste	Paste is directly rubbed at the site	Khan et al. (2009), Shaheen et al. (2012)
Whole plant	Abortion			
Leaves	Cuts and wounds	Paste	Paste is directly applied	Bhatt and Negi (2006), Ahmad et al. 2016a, b
Whole plant	Bloody dysentery	Juice	NAD[a]	Manandhar (2002)
Leaves	Astringent	Juice	Leaves are directly eaten	Ali and Qaiser (2009)

(continued)

Table 6.2 (continued)

Part used	Indication	Herbal preparation	Dosage form	References
Leaf	Fungal infection	Paste	Leaf paste is applies at the site	Uniyal and Shiva (2005)

[a]NAD not appropriately described

important for production of energy, growth and other functions. This plant is rich source of carbohydrates and fibre. Protein, moisture content, ash content and fats were also recorded (Hameed and Dastagir 2009; Singh et al. 2013a, b). Mineral elements though usually form a small portion of total composition of plant materials; they are nevertheless of great physiological importance particularly in the body metabolism (Bamiro et al. 1995). The elemental analysis in different parts of plant was carried out, and the concentrations are shown in Table 6.3 (Hameed et al. 2008).

6.5 Contraindication

Significant levels of oxalic acid are present in the plants, which gives the leaves of numerous individuals from this variety an acidic lemon flavour. Though completely alright in little amounts, the leaves ought not be eaten in huge amounts since the oxalic acid can secure up different supplements in the food, particularly calcium, along these lines causing mineral inadequacies. When the plant is cooked, the concentration of oxalic acid gets, however, decreased. Therefore, individuals with a propensity to rheumatism, arthritis, gout, kidney stones, or hyperacidity should take particular alert if considering this plant for their eating regimen, since it can bother their condition (Bown 1995).

6.6 Physicochemical Standardization

See Fig. 6.1 and Table 6.4.

6.6.1 Macroscopical Characters

6.7 Phytochemistry

A comprehensive literature survey on phytochemical investigations of *R. hastatus* reveals that the chemical constituents reported from this plant are from different classes of secondary metabolites that include flavonoids, anthraquinones, phenolic

Table 6.3 Elemental analysis of different parts of *Rumex hastatus*

Plant part	C	O	Na	Mg	Al	Si	S	P	Cl	K	Ca	Fe
Root	44.78	44.78	0.38	0.55	0.44	1.20	0.33	0.27	0.95	3.21	2.77	0.52
Stem	42.48	42.48	0.59	0.46	0.20	1.32	0.45	0.27	1.61	6.10	1.51	0.58
Leaf	38.32	41.82	0.26	1.43	1.24	4.26	0.47	0.39	0.68	6.09	3.28	1.65
Petiole	36.11	50.34	–	–	2.12	4.56	–	–	–	3.17	3.70	–
Flower	47.57	48.00	–	0.77		0.79	–	–	–	–	2.87	–

Fig. 6.1 Aerial parts of *Rumex hastatus* at its flowering stage

Table 6.4 Physicochemical determination of *Rumex hastatus*

Analytical parameter	Value (% W/W)
Ash values	
Total ash	13.78
Water-soluble ash	0.58
Acid-insoluble ash	0.77
Sulphated ash	2.3
Extractive values	
Water soluble (hot)	12.6
Ethanol soluble (hot)	4.90
Water soluble (cold)	1.32
Ethanol soluble (cold)	0.56
Successive extractives	
Petroleum ether	0.23
Chloroform	0.38
Ethyl acetate	2.2
Methanol	14.3
Aqueous	5.27
Loss on drying	7.6
Foaming index	<100
Swelling index	5 mL
Haemolytic value	10.48
Crude fibre content	20.63

compounds, naphthalenes and various other constituents given in Table 6.5 (Zhang et al. 2009; Sahreen et al. 2014).

R. hastatus is differentiated by the presence of various secondary phytoconstituents. There are over 20 compounds which have been isolated from this plant. In roots the most abundant phytoconstituents are the anthraquinones and

Table 6.5 Qualitative phytochemical screening of *Rumex hastatus*

Part used	Constituent	Extract	Reference
Bark	Tannins	Aqueous	Akhtar and Mirza (2018)
Bark	Coumarins	Methanol/ chloroform	Shafiq et al. (2017), Akhtar and Mirza (2018)
Bark	Alkaloids	Aqueous	Akhtar and Mirza (2018)
Bark	Saponins	Aqueous	Akhtar and Mirza (2018)
Whole plant	Steroid	Chloroform	Shafiq et al. (2017)
Whole plant	Flavonoid	Methanol	Shafiq et al. (2017)
Whole plant	Anthraquinone glycoside	Methanol	Shafiq et al. (2017)
Whole plant	Cardiac glycosides	Ethanol	Shafiq et al. (2017)
Root	Terpenoids	Methanol	Sahreen et al. (2015)
Root	Phlobatannin	Methanol	Sahreen et al. (2015)

Table 6.6 Macroscopical characters

Characters	Observations	References
Taste	Leaves are sour in taste. The roots possess characteristic taste and odour	Singh et al. 2013a, b, 2014)
Size	Length 20–30 cm, diameter 2–5 mm	Wallis (1997)
Colour	Greenish yellow	
Shape	Regular branched	
Fracture	Short	
Odour	Characteristic	
Surface characters	Smooth	

their derivatives (Sharma et al. 2018). By UPLC-DAD method, various anthraquinone derivatives have been isolated from the methanol extract of aerial and root part. A phytochemical investigation on roots also led to the isolation of some naphthalenes by column chromatography as reported by Zhang et al. (2009). Apart from naphthalenes and anthraquinones, the other constituents isolated from *R. hastatus* are flavonoids. These are the polyphenolic compounds having potential antioxidant properties (Schlachterman et al. 2008). HPLC on the alcoholic extract of root and leaf and column chromatography of the root extract led to the isolation of some flavonoids (Zhang et al. 2009; Sahreen et al. 2011; Sahreen et al. 2014). Moreover, new fatty acid esters and phenolic glucosides were isolated and identified from the aerial parts of *R. hastatus* by column chromatography for the first time (Sultana et al. 2017). The isolated compounds and their nature are given in Tables 6.6 and 6.7, and their structures are shown in Figs. 6.2, 6.3, and 6.4.

Table 6.7 Chemical constituents isolated from *Rumex hastatus*

Chemical class	Constituent	IUPAC	Extract	Reference
1. Flavanoids				
	(1a) Rutin	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-[[(2*R*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one	95% EtOH root extract	Zhang et al. (2009), Sahreen et al. (2011)
	(1b) Luteolin	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxychromen-4-one	95% MeOH leaf and root extract	Sahreen et al. (2011, 2014)
	(1c) Luteolin-7-O-glucoside	2-(3,4-Dihydroxyphenyl)-5-hydroxy-7-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	95% MeOH leaf and root extract	Sahreen et al. (2011, 2014)
	(1d) Kaempferol	3,5,7-Trihydroxy-2-(4-hydroxyphenyl) chromen-4-one	95% MeOH leaf and root extract	Sahreen (2011, 2014)
	(1e) Vitexin	5,7-Dihydroxy-2-(4-hydroxyphenyl)-8-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one	95% MeOH root extract	Sahreen et al. (2014)
2. Anthraquinones				
	(2a) Emodin	1,3,8-Trihydroxy-6-methylanthracene-9,10-dione	80% MeOH root extract	Liang et al. (2010), Sharma et al. (2018)
	(2b) Physcion	1,8-Dihydroxy-3-methoxy-6-methylanthracene-9,10-dione	95% MeOH aerial extract	Liang et al. (2010), Sharma et al. (2018)
	(2c) Chrysophanol	1,8-Dihydroxy-3-methylanthracene-9,10-dione	80% MeOH root extract	Sharma et al. (2018)

(continued)

Table 6.7 (continued)

Chemical class	Constituent	IUPAC	Extract	Reference
	(2d) Emodin-8-O-β-D-glucopyranoside	1,6-Dihydroxy-3-methyl-8-(((3R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl) oxy)anthracene-9,10-dione	80% MeOH root extract	Sharma et al. (2018)
	(2e) Chrysophanol-8-O-β-D-glucopyranoside	1-Hydroxy-3-methyl-8-(((3R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)anthracene-9,10-dione	80% MeOH root extract	Sharma et al. (2018)
3. Phenolic glucosides				
	(3a) Hastatuside A	7-Hydroxy-5-methyl-4-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-2-one	95% EtOH root extract	Zhang et al. (2009)
	(3b) Hastatuside B	[(2*R*,3*S*,4*S*,5*R*,6*S*)-6-(7-acetyl-8-hydroxy-6-methylnaphthalene-1-yl)oxy-3,4,5-trihydroxyoxan-2-yl]methyl acetate	95% EtOH root extract	Zhang et al. (2009)
4. Stilbenoids				
	Resveratrol	5-[(*E*)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol	95% EtOH root extract	Zhang et al. (2009)
5. Napthalenes				
	(5a) Rumexoside	6-Acetyl-5-hydroxy-7-methyl-4-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxynaphthalene-2-carboxylic acid	95% EtOH root extract	Zhang et al. (2009)
	(5b) Nepodin	1-(1,8-Dihydroxy-3-methylnaphthalen-2-yl) ethanone	95% EtOH root extract	Zhang et al. (2009)
	(5c) Torachryson-8-ylβ-D-glucopyranoside	1-(1-Hydroxy-6-methoxy-3-methyl-8-(((3R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl) oxy)napthalen-2-yl)ethanone	95% EtOH root extract	Zhang et al. (2009)

	(5d) Orientaloside	1-[8-[(2*S*,3*R*,4*S*,5*R*,6*R*)-3,5-dihydroxy-6-(hydroxymethyl)-4-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] oxyoxan-2-yl]oxy-1-hydroxy-3-methylnaphthalen-2-yl]ethanone	95% EtOH root extract	Zhang et al. (2009)
6. Ester				
Fatty ester	**(6a)** Tridecyl oleate	Tridecyl (*Z*)-octadec-9-enoate	MeOH extract of aerial parts	Sultana et al. (2017)
Aromatic ester	**(6b)** 3′,4′-Dihydroxybenzyl oleate	Heptadec-8-en-1-yl 2-(3,4-dihydroxyphenyl) acetate	MeOH extract of aerial parts	Sultana et al. (2017)
Sterol ester	**(6c)** β-Sitosteryl linoleate	[(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-[(2*R*,5*R*)-5-ethyl-6-methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[a]phenanthren-3-yl] (9*Z*,12*Z*,15*Z*)-octadeca-9,12,15-trienoate	MeOH extract of aerial parts	Sultana et al. (2017)
Steroidal ester	**(6d)** β-Sitosterol l3-benzylether 3′-capriate	5-Ethyl-2-hydroxyphenyl deconate	MeOH extract of aerial parts	Sultana et al. (2017)
	(6e) β-Sitosterol 3-benzyl ether 3′- oleate	5-Ethyl-2-hydroxyphenyl octadec-9-enoate	MeOH extract of aerial parts	Sultana et al. (2017)
	(6f) β-Sitosterol 3-(3′,4′-dihydroxybenzyl)ether 3′-linoleate	β-Sitosterol 3-(3′,4′-dihydroxybenzyl)ether 3′-linoleate	MeOH extract of aerial parts	Sultana et al. (2017)
Steroidal tetragalactoside	**(6g)** β-Sitosterol- 3β-benzyl 3′-oxy-3′-O-β-D-galactopyranosyl-(6a → 1b-)O-β-D-galactopyranosyl-(6b → 1c)-O-D-galactopyranosyl-(6c → 1d)-O-β-D-galactopyranosyl- 2d-capriate	β-Sitosterol-3β-benzyl 3′-oxy-3′-O-β-D-galactopyranosyl-(6a → 1b-)O-β-D-galactopyranosyl-(6b → 1c)-O-D-galactopyranosyl-(6c → 1d)-O-β-D-galactopyranosyl- 2d-capriate	MeOH extract of aerial parts	Sultana et al. (2017)
7. Others				
Phenolic pentaxyloside	**(7a)** 1-Undecan oxy-3-phenol-3-O-β-D-xylopyranosyl-(2a → 1b)-O-β-D -xylopyranosy l-(2b → 1c)-O-β-D-	1-Undecan oxy-3-phenol-3-O-β-D-xylopyranosyl-(2a → 1b)-O-β-D-xylopyranosyl-(2b → 1c)-O-β-D-	MeOH extract of aerial parts	Sultana et al. (2017)

(continued)

Table 6.7 (continued)

Chemical class	Constituent	IUPAC	Extract	Reference
	xylopyranosyl-(2c → 1d)-O-β-D-xylopyranosyl-(2d → 1e)-O-β-D-xylopyranoside,	xylopyranosyl-(2c → 1d)-O-β-D-xylopyranosyl-(2d → 1e)-O-β-D-xylopyranoside		
α-L-Hexaglucoside derivative	**(7b)** α-L-glucopyranosyl-(2a → 1b)-O-α-L-glucopyranosyl-(2b → 1c)-O-α-L-glucopyranosyl-(2c → 1d)-O-α-L-glucopyranosyl-(2d → 1e)O- α-L-glucopyranosyl-(6e → 1f)-O-α-L-glucopyranoside	α-L-glucopyranosyl-(2a → 1b)-O-α-L-glucopyranosyl-(2b → 1c)-O-α-L-glucopyranosyl-(2c → 1d)-O-α-L-glucopyranosyl-(2d → 1e)O-α-L-glucopyranosyl-(6e → 1f)-O-α-L-glucopyranoside	MeOH extract of aerial parts	Sultana et al. (2017)

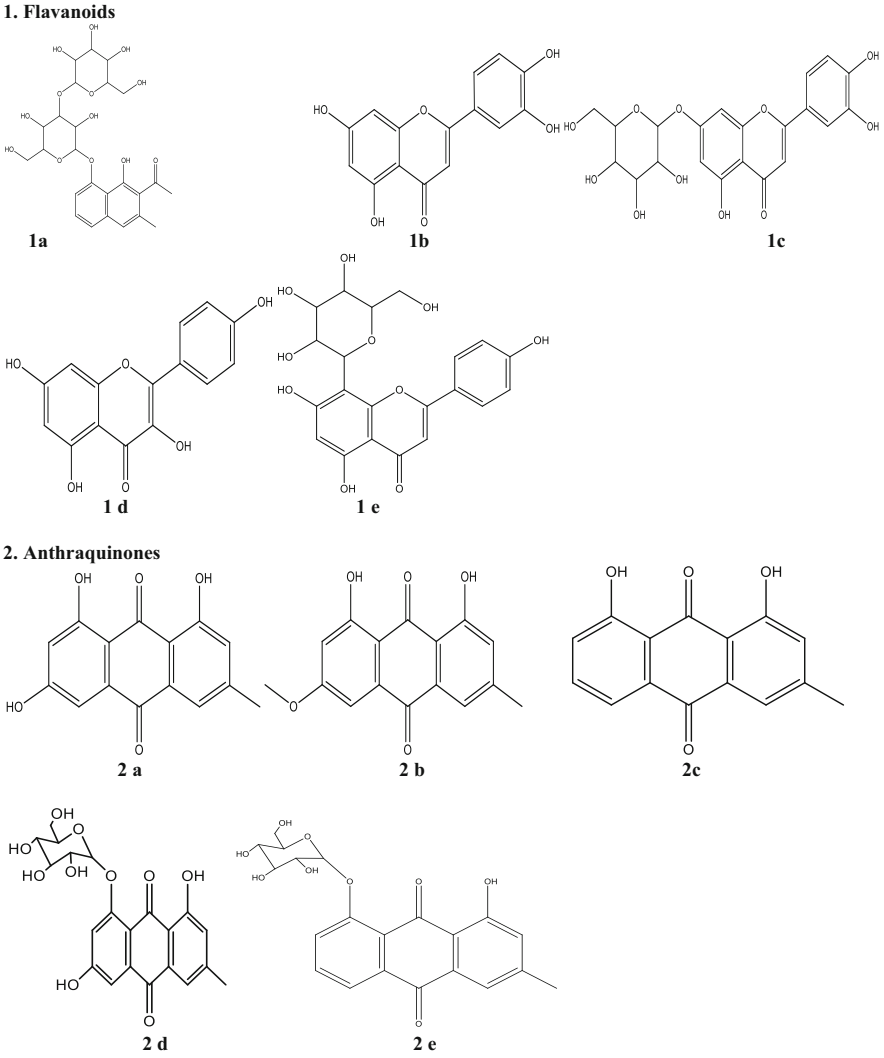
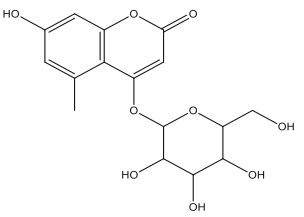
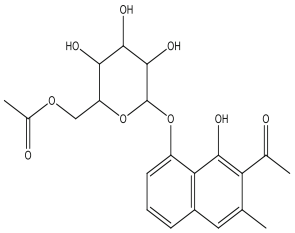


Fig. 6.2 Chemical structures of some isolated compounds from various extracts of *R. hastatus*

3. Phenolic glucosides

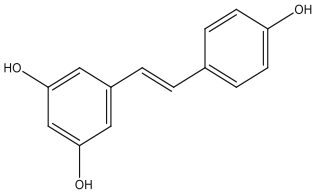


3 a



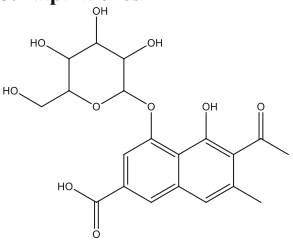
3 b

4. Stilbenoids

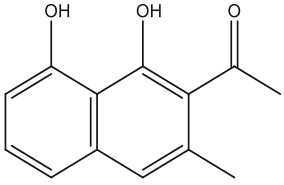


4

5. Napthalenes



5 a



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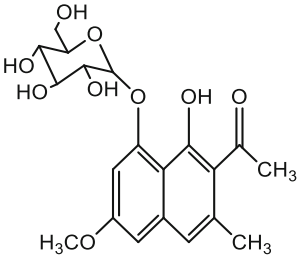
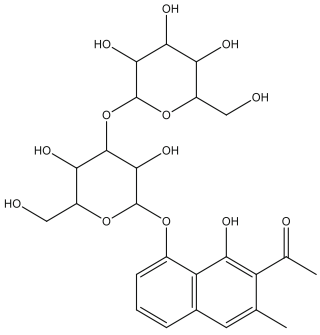


5 c



5 d

Fig. 6.2 (continued)

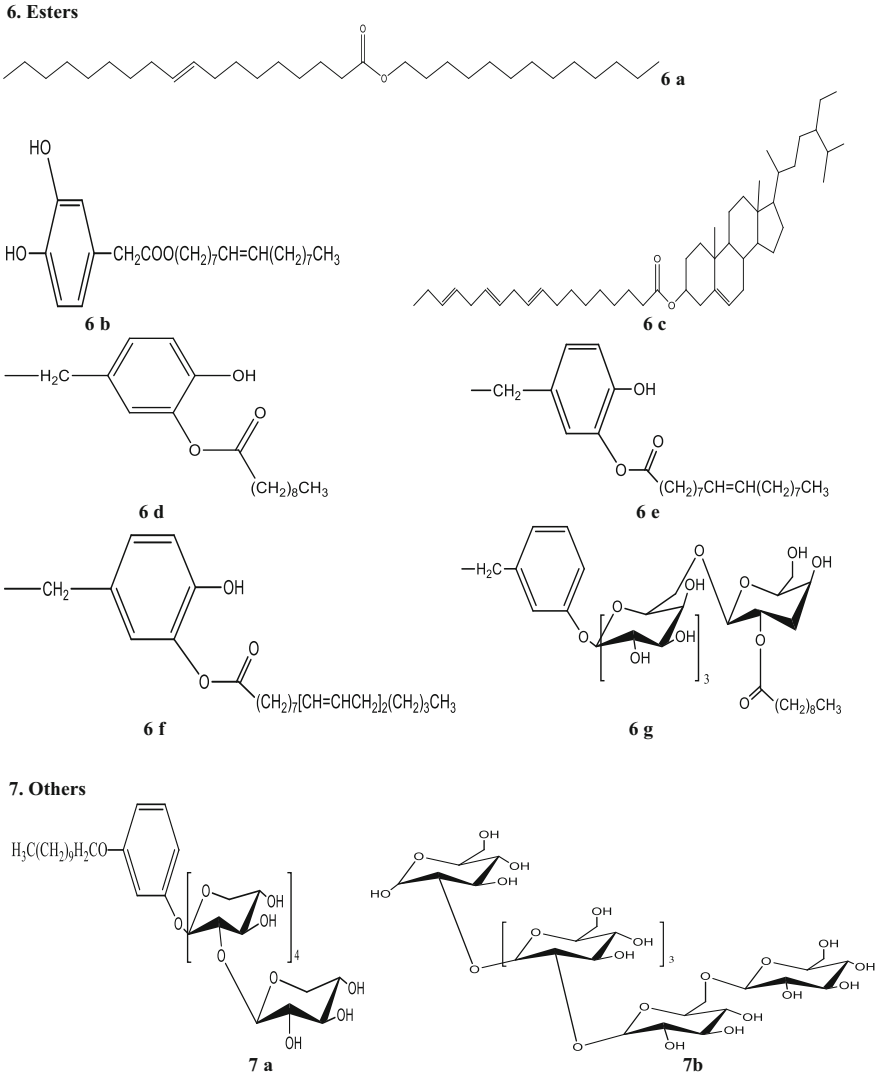


Fig. 6.2 (continued)

6.8 Pharmacology

Plants are well-known excellent perspectives for the discovery of new therapeutical products. The World Health Organization (WHO) estimates that 65–80% of the population of the developing countries depends on medicinal plants for basic pharmaceutical care (Singh et al. 2013c). The fact the plants are prominent origins

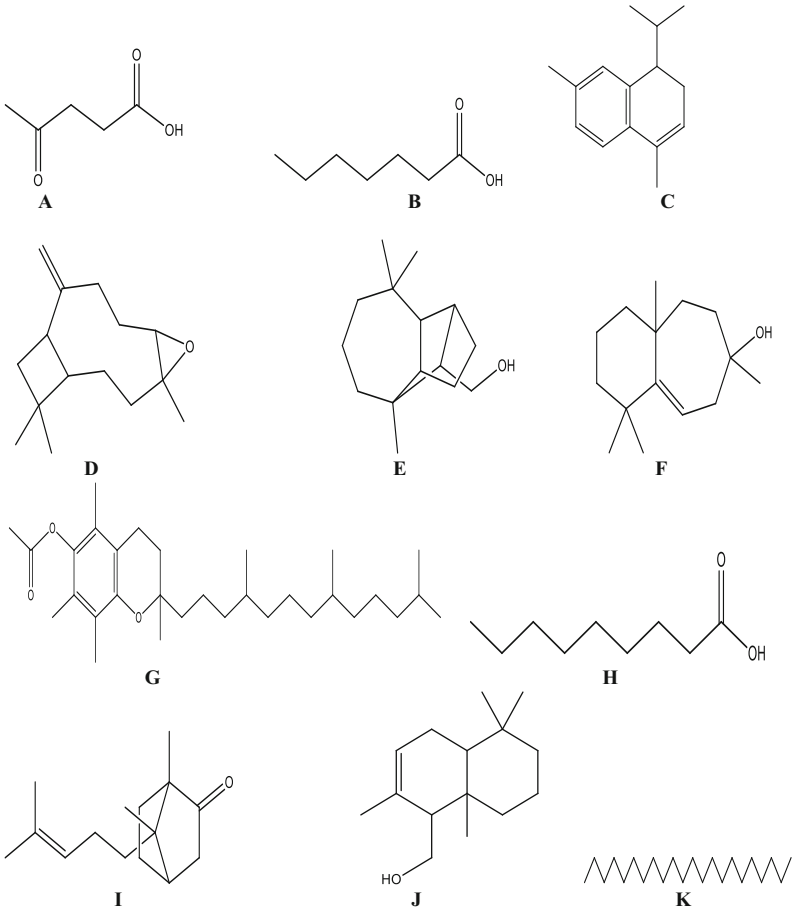


Fig. 6.3 Chemical structures of some identified components of essential oil of *R. hastatus*. (**a**) Levulinic acid; (**b**) Enanthic acid; (**c**) α–calcorene; (**d**) Caryophyllene oxide; (**e**) Isolongifol; (**f**) Widdrol; (**g**) Pelargonic acid; (**h**) Vitamin; (**i**) Campherenone; (**j**) Drimenol; (**k**) Docosane

for new bioactive principles is established and hence has wide utility in therapeutics (Kinghorn et al. 2011). Different parts of the medicinal plants have been utilized for various therapeutic purposes in folk medicine. Indeed, many of the plants and their preparations have been recorded to be used to treat different maladies and promote healing (Sen et al. 2010).

6.8.1 Anti-Nociceptive

The occurrence of tissue damage to the body is informed by means of a warning system called as pain (Nickel et al. 2012). Since pain modulation is an intricate

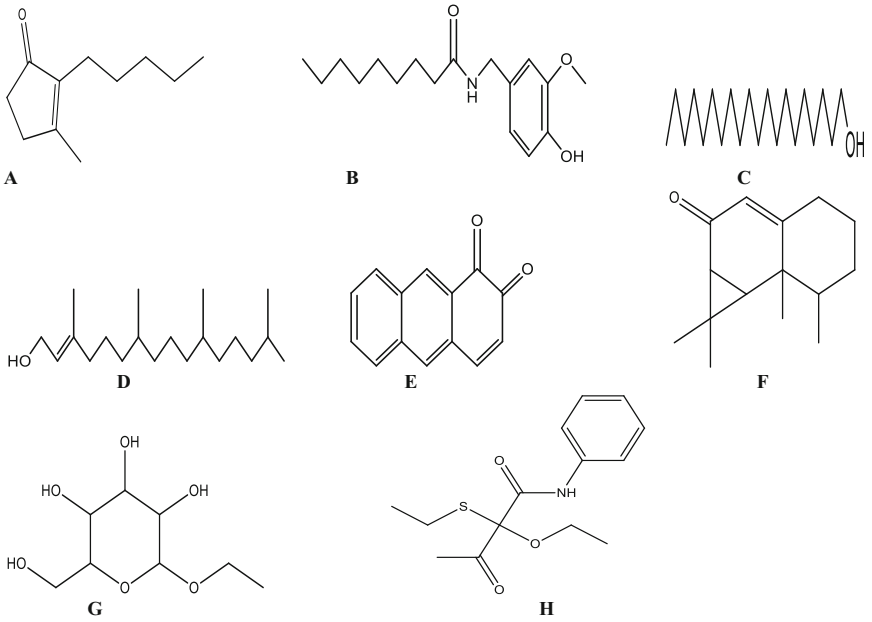


Fig. 6.4 Chemical structures of anticancer compounds identified in the GC-MS of chloroform fraction of *R. hastatus*. (**a**) Dihydrojasmone; (**b**) Nonivamide; (**c**) Eicosanol; (**d**) Phytol; (**e**) Anthracenedione; (**f**) Aristolone; (**g**) Ethyl alpha-d-glucopyranoside; (**h**) 2-Ethylthio-2-ethoxy-3-oxo-N-phenylbutanamide

process involving many mediators and receptors at the peripheral and central levels, its management using the available analgesics could not completely thrive well. Nociceptive neuron sensitivity is adjusted by a large variety of mediators in the extracellular space which either include neurotransmitters or neuromodulators in turn activating a large number of receptors and therefore a cascade of events controlling the perception of pain (Julius and Basbaum 2001; Scholz and Woolf 2002; Lewin et al. 2004; Hucho and Levine 2007; List 2010). Identification of the components involved in the complex process is undertaken worldwide, and attempts are being made to develop new agents that act on these components (Bektas et al. 2015). Analgesic drugs such as opiates that are currently available are not useful in all the cases as their beneficial effects are superseded by their various adverse effects (Zendehdel et al. 2011). Therefore, there is an urgent need of new analgesic drugs with promising pharmacological actions. In addition, the revelation of plant-based drugs with high restorative viability, however less or, perhaps, no toxicity, may be beneficial as substitutions to customary analgesics like narcotics and NSAIDs (Sen et al. 2010). Singh et al. (2013a, b) evaluated the anti-nociceptive potential of *R. hastatus*. The study involved the use of acetic acid-induced writhing method, tail flick model and formalin-induced pain model in mice, for establishing anti-nociceptive activity of the ethanol and aqueous extract of stem and root, using standard drugs. The study revealed that the minimum (200 mg/kg) and maximum

(400 mg/kg) doses of the aqueous and ethanol extract of root and stem showed significant inhibition in mice in acetic acid-induced abdominal constrictions. Maximum inhibition was shown by the ethanolic extract (400 mg/kg) of root in abdominal constrictions in mice induced by acetic acid, and the effect was comparable to that produced by indomethacin. Taken together, the above results indicated that peripheral and central analgesic activity is exhibited by aqueous and ethanol extracts of both root and stem of *R. hastatus*. However, out of aqueous and ethanolic extracts, the former is more active. Both phases of the formalin-induced pain are inhibited with a more pronounced effect on the second than the first phase. Both central and peripheral effects are confirmed from the study. The results observed from both tail flick test and acetic acid-induced abdominal constrictions were found to be significant.

6.8.2 Antipyretic

When the body reaches to a temperature above normal, the condition is called as fever or pyrexia. An antipyretic is a kind of drug that will forestall or decrease fever by bringing down internal heat level from a raised state. Nonetheless, the "normal" temperature can fluctuate from individual to individual inside specific boundaries. By and large, most non-steroidal anti-inflammatory drugs (NSAIDs) work by repressing prostaglandin synthetase inside the nerve centre (Deshpande et al. 2003). Most of the antipyretic drugs cause inhibition of prostaglandin E2 (PGE2) biosynthesis and Cox-2 expression which in turn causes reduction in elevated body temperatures. Most of these agents are toxic to the hepatic cells, cortex of brain, glomeruli, and heart muscles, but they have high selectivity to inhibit Cox-2 in an irreversible manner, while the selectivity is lower for the natural Cox-2 inhibitors but with lesser toxic effects (Bouldin et al. 1999). Microbes including bacteria and viruses are the causative agents of fever setting off the body's defence system (Deshpande et al. 2003). Pain and pyrexia are frequently associated with infections and ailments. The drugs generally prescribed include the non-steroidal anti-inflammatory drugs (NSAIDs) which however have huge gastrointestinal side effects like peptic ulcer perforations, bleeding and obstructions restricting their uses in clinical settings (Ofman et al. 2002; Castellsague et al. 2012). Since there are fewer propensities for herbal drugs to cause any toxicity, therefore there is a huge demand of the same. Further there is an increase in the health-care costs which in turn influences people to find newer and natural low-cost alternatives (Bouldin et al. 1999).

Singh et al. (2013a, b) evaluated stem and roots of *R. hastatus* for its antipyretic activity using yeast-induced pyrexia in rats and was performed on the ethanolic and aqueous extracts of the plant. In hyperthermic rats, at the dosage of 400 mg/kg, the ethanolic extracts of both the parts produced a pronounced antipyretic effect in a dose-dependent manner when compared with untreated rats. The results were proportionate with the standard drug, paracetamol (150 mg/kg). This consequently confirmed that *R. hastatus* possessed significant antipyretic potential.

6.8.3 Anti-Inflammatory

The act of utilizing plants, their parts, or concentrates as anti-inflammatory mixture is known since ancient times (Khalifa 2004). When infectious microorganisms, for example, viruses, fungi or bacteria, attack the body, dwell specifically in tissues and additionally flow in the blood, inflammation takes place (Artis and Spits 2015; Isailovic et al. 2015; Pedraza-Alva et al. 2015). There are two principal classes of inflammatory substances: anti-inflammatory mediators and pro-inflammatory mediators. Moreover, some mediators possess both properties of anti- and pro-inflammation (Vignali and Kuchroo 2012). Cytokines (e.g. tumour necrosis factor, α interleukins and interferons), chemokines which include monocyte chemoattractant protein 1 and eicosanoids (e.g. leukotrienes and prostaglandins) are widely concentrated in relationship with the pathological states among the cellular pathways and inflammatory mediators. A significant pro-inflammatory cytokine which is discharged from different cells and applies numerous cell effects includes the tumour necrosis factor (TNF)-α, which is an effective inflammation-regulating transcription factor (Montgomery and Bowers 2012; Zelová and Hošek 2013). Nevertheless anti-inflammatory medications are frequently connected with serious toxic effects, for example, peptic ulcers and gastrointestinal bleeding (Alwashli et al. 2012). Many natural drugs isolated from medicinal plants are considered as successful and more secure for the treatment of different ailments including inflammation (Stevenson and Hurst 2007).

The aqueous and ethanol extracts of roots and stem of *R. hastatus* were evaluated for anti-inflammatory activity (Singh et al. 2013a, b). This in vivo study made use of two common models cotton pellet-induced granuloma and carrageenan-induced paw oedema method at a dose of 400 mg/kg; the ethanolic concentrates of both root and stem (400 mg/kg) of *R. hastatus* happened to show more critical mitigating action than the lesser 200 mg dosages, in experimenting animals, following 3 hours of medication treatment. Dose-dependent anti-inflammatory action was prominent, which was comparable to the standard drug indomethacin, following 6 hours of drug treatment. Further, inhibition in rise of dry weight of cotton pellet-induced granuloma was shown by stem as well as root extracts of *R. hastatus* in the second method used. However, ethanol extract of the root showed the greatest per cent inhibition at 400 mg/kg of drug treatment, with the ethanol extract of the stem at the same dose trailing behind and the aqueous extract being least effective. The carrageenan-induced paw oedema method was used to evaluate the acute inflammatory activity. Carrageenan (a sulphated polysaccharide belonging to the family Rhodophyceae) is obtained from a seaweed and is most widely used to produce biphasic acute inflammation. The liberation of serotonin and histamine marks the first phase (about 1 hour), while the liberation of prostaglandin, bradykinin, lysosome and protease marks the second phase, which exceeds 1 hour. The second accelerating phase of swelling relation is measured after 3 hours, wherein prostaglandins play the significant role (Hernández-Pérez and Rabanal 2002). This study reveals that *R. hastatus* extracts exhibited inhibition of oedema, through all the phases of inflammation; nonetheless the effectiveness in the proliferative phase of

inflammation was confirmed by the prominent contraction of cotton pellet granuloma by all the extracts. The outcome of this study strongly indicates the anti-inflammatory potential of *R. hastatus* which however requires more exploration.

6.8.4 Antioxidant and Antiradical

Impressive consideration has been given to phenolics and flavonoids within enzymatic and non-enzymatic antioxidant components. Plants are expected to be a source of common antioxidant principles exhibiting significant antioxidant action and may assist with ensuring cells against the oxidative harm brought about by free radicals (Kähkönen et al. 1999). The hydroxyl and conjugated ring structures which are present in phenolic compounds have the ability of preventing oxidation through hydrogenation or complexing with oxidizing species and in turn scavenging free radicals (Shahidi et al. 1992). Along these lines, the medicinal plants have promising antioxidant compounds to be tried as antiradical drugs for the cure of illnesses arising because of oxidative pressure. The valuable impacts of antioxidant compounds have been confirmed in a few trial and epidemiological investigations (Ruch et al. 1989; Babu et al. 2001).

Sahreen et al. (2011) conducted a study to evaluate the antioxidant potential of different fractions of leaves of *R. hastatus*. The study found out that the ethyl acetate fraction of the plant contained high amount of total polyphenolics and exhibited promising potential of scavenging for ABTS radicals and hydroxyl radicals as well as prevention of β-carotene linoleic acid peroxidation, while butanolic fraction contained high flavonoid content and reflected most promising iron chelation, DPPH, and phospho-molybdate scavenging activity. However, scavenging of hydrogen peroxide by the chloroform fraction reflected its most potent antioxidant potential, although the antioxidant potential of methanolic and ethyl acetate fractions was found to be lower than that of standard.

Since no antioxidant studies had been conducted on the roots of *R. hastatus*, therefore (Sahreen et al. 2015) hypothesized that being an important ethnopharmacological part of the plant, the roots must have potential antioxidant activity, and henceforth designed an in vitro study on the same using different fractions. The results revealed that all the isolated fractions of the extract exhibited dose-dependent activity. The methanol and the butanol fractions showed the highest antioxidant potential, except hydrogen peroxide radical scavenging assay where highest scavenging activity was found in the chloroform fraction. Significant beta-carotene linoleic acid was found in the aqueous fraction, with the least potential shown by ethyl acetate and n-hexane fractions. Further analysis in both the studies carried on by Sahreen et al. on the ethyl acetate fraction suggested the presence of kaempferol, luteolin, rutin and luteolin-7-O-glucoside and vitex might probably be the source of antioxidant potential of the plant (Sahreen et al. 2011; Sahreen et al. 2015).

Similar findings were found by Ahmad et al. (2015), when their study on the antioxidant potential of *R. hastatus* revealed strong antioxidant capability of crude

saponin and flavonoid extract obtained by fractionation of methanol extract of *R. hastatus*; ABTS free radical scavenging, DPPH, and hydrogen peroxide assays were used. Moreover the current study showed that the flavonoid fraction of the plant possessed highest antioxidant activity, and since the previous studies had revealed that the fractions exhibiting promising antioxidant potential contained flavonoids and phenols, it goes parallel with the fact that they may be credible for the drug possessing antioxidant potential, as reported (Sahreen et al. 2011; Afzal et al. 2014).

In one more investigational study executed by Ahmad et al. (2016a, b), the volatile oil of *R. hastatus* was put under surveillance, the results of which proved that the volatile oil of the plant was an antioxidant source in the free radical scavenging assay, which was significant and comparable with the positive control. Taken together, the results of all the studies clearly demonstrate the high antioxidant potential of *R. hastatus*, which after subjecting to development of new drug candidates can be helpful in numerous pathological states linked to oxidative stress and generation of free radicals.

6.8.5 Hepatic Protective Effect

The liver plays out an assortment of significant host safeguard and metabolic activities that incorporate gluconeogenesis, detoxification, production of acute phase proteins, expulsion of endogenous mediators, emission of favourable pro-inflammatory cytokines, etc. (Pastor et al. 1995). It is a remarkable organ because of the fact that the loss of liver cells due to medication toxicity or different abuse can be overwhelmed by recovery (Mehendale 2005). Numerous reports uncovered that the free radicals created during hepatic damage exhausted the levels of the enzyme and non-enzyme framework which are connected to liver wounds (Liu et al. 2006).

A study was designed by Sahreen et al. (2013) on the leaves of *R. hastatus* to analyse their hepatoprotective activity, using methanol and its fractioned extracts hexane, butanol, chloroform, ethyl acetate and aqueous extract against carbon tetrachloride (CCl_4), the agent causing hepatotoxicity in rats. The glutathione reserves as well as the activity of enzymes involved in oxidation were depleted, while the lipid peroxides, DNA and histopathological injuries were elevated by administration of CCl_4. Moreover the hepatic damage like necrosis, fatty changes, Kupffer cell infiltration and cellular hypertrophy was also caused. When the different fractions of leaves of *R. hastatus* (200 mg/kg body weight) were supplemented, attenuation in the toxicity was noted in the liver tissues as the numerous parameters like enzymatic, histological and serological were normalized. Per cent DNA fragmentation and ladder assay were performed which clearly indicated the amelioration of hepatic damage and oxidative stress induced by CCl_4.

Another similar study was undertaken by Sahreen et al. (2017) in order to explore the hepatoprotective nature of *R. hastatus* roots, using methanol and ethyl acetate extracts. Again, CCl_4 was used as the agent to trigger hepatotoxicity which was checked over by different liver function markers including alkaline phosphatase,

γ-glutamyltransferase, aspartate transaminase, alanine transaminase and lactate dehydrogenase. Also lipid profile was assessed by the amount of triglycerides, HDL, LDL and serum TC. Furthermore DNA and cell damages and enzyme activities were also assessed. After the co-administration of the different extracts of roots of *R. hastatus*, the lipid profile, liver function markers and cellular and DNA damages were restored in rats. The oxidation status was also improved revealing that the roots of *R. hastatus* are a strong source of antioxidant activity and have the capacity to restore liver from the toxicity and fibrosis caused by CCl_4. This is a clear indication that the plant reflects promising treatment of ailments regulated by markers controlling oxidation as well as free radical-mediated pathological states and hence is a good drug candidate to be explored for hepatic ailments due to its hepatoprotective potential.

6.8.6 Anticholinesterase

The most widely recognized neurological diseases are depression, Alzheimer's disease, epilepsy, anxiety, madness, susto (fear), numbness, insomnia, migraine, headache, stress, Parkinson's disease and so on (Bourbonnas-Spear et al. 2005; Aarsland et al. 2008). Depending on their traditional knowledge, large quantities of normal therapeutically active components have been extracted from different medicinal plants. For instance, the *Ginkgo biloba* was scientifically verified as anti-ageing and was customarily seen as memory enhancer, which however was established for treating Alzheimer's disease (mild or moderate) (Burkard and Lehrl 1991; Kanowski et al. 1996; Le Bars et al. 1997). Essential oils are comprehended to possess major significance as they can neutralize free radicals, which are produced in the process of metabolism of oxygen (Ruberto and Baratta 2000). ROS are liable for many ailing conditions which include nervous diseases and oxidative pressure (Kumar et al. 2012). They are also known for their scavenging potential and effectiveness in many cognitive conditions. Among the psychological issues, the disease called Alzheimer's disease (AD) is widely recognized in old individuals (Mukherjee et al. 2007). One helpful methodology for AD is to build the centralization of the synapse (acetylcholine) by hindering the protein (acetylcholinesterase) liable for its breakdown. Different medications of plant origin as well as chemical origin have been utilized for the regulation of Alzheimer's and different apprehensive diseases (Small et al. 1997).

Ahmad et al. (2015) conducted a study aiming to investigate the potential of *R. hastatus* using various fractions, viz. chloroform, n-hexane, ethyl acetate, crude saponins, aqueous fraction, methanol extract and flavonoids for acetylcholinesterase and butyrylcholinesterase inhibition at various concentrations (125, 250, 500, 1000 μg/mL) in order to substantiate its traditional uses in neurological disorders, using Ellman's spectrophotometric analysis. Concentration-dependent cholinesterase inhibition was shown by all the extracts with radical scavenging potentiality. Saponins and flavonoids reflected the highest potential inhibition, while moderate to high potential inhibition was reflected by the subsequent fractions.

In the same manner, potential against butyrylcholinesterase inhibition of different plant extracts was also carried out. Therefore, the strong anticholinesterase potential of saponin and flavonoid extracts as well as the other fractions of *R. hastatus* confirmed claimed ethnomedicinal properties and established the potential of *R. hastatus* in the era of nervous disorders. Also the activity of extracts was comparable to that of positive control, galantamine. Furthermore, the study also revealed that the saponin and the flavonoid extracts exhibited the most prominent activity based on the enzyme (AChE, BChE) inhibition as well as radical scavenging potential, which also directed to the fact that the plant is a potent source of anticholinesterase compounds, which are most probably the saponins and flavonoids. This as well is supported by the fact that the saponins are also significant secondary metabolites, verified to be beneficial in different pharmacological activities. For example, traditional Chinese drugs are a source of saponins, demonstrating remarkable antioxidant potential (Xi et al. 2008). Also the saponins known as bacosides isolated from *Bacopa monnieri* and the flavonoids known as ginkgo flavon glycosides isolated from *Ginkgo biloba* possess the said activities (Das et al. 2002).

In another study conducted by Ahmad et al. (2016a, b), the isolation of essential oil from *R. hastatus* was done, which after assessment indicated that the plant is a potential source of significant volatile principles possessing anticholinesterase potential. The essential oil was subjected to the anticholinesterase assay performed against acetyl cholinesterase (AChE) and butyrylcholinesterase (BChE) at different concentrations (62.5–1000 μg/mL). The results were however comparable with the positive control taken as galanthamine. Results of the study strongly indicate the anticholinesterase potential of essential oil. A clear conclusion could be drawn that *R. hastatus* as an important source of constituents may perhaps result in therapy development and neutralize free radicals as well as rehabilitate neurodegenerative disorders. The most common constituents isolated from *R. hastatus* during the study include the following: palmitic acid, methyl palmitate, myristic acid, capric acid, pelargonic acid, drimenol, cetane, docosane, velleral, isolongifolol, neophytadiene, acetone, widdrol and levulinic acid. After exploring the different constituents of essential oil obtained, it was concluded that the significant anticholinesterase activity of the volatile oil was due to the presence of various phytoconstituents present. It was also found that the prominent activity of *R. hastatus* might be attributed to its hydrophobic nature due to its significant affinity towards the hydrophobic site of AChE, which is also the active site (Steinberg et al. 1975; Loizzo et al. 2008). Various phytoconstituents of volatile oil have also been brought to light by other investigators previously, possessing antiradical and anticholinesterase activities (Yi and Kim 1982; Stamatis et al. 1999; Decker et al. 2005; Mehendale et al. 2008; Öztürk et al. 2011; Sengupta and Ghosh 2012).

6.8.7 Anti-Tumour and Angiogenic Potential

Tumour is primarily described by unusual and unnecessary multiplication of cells, which dynamically disturb the cells in the neighbourhood. The formation of new blood vessels which is called the angiogenesis likewise happens alongside the multiplication of cells which happens in ordinary tissues very rarely, besides embryogenesis and wound repairing (Folkman 1992). It has been clearly showed that exorbitant angiogenesis prompts a few pathological states including ovarian cyst atherosclerosis, cancer, arthritis and osteomyelitis (Carmeliet and Jain 2000). Different chemotherapeutic substances are utilized against the pathophysiological conditions, which are angiogenesis dependent, particularly against tumour. Due to plenty of dangerous impacts of these agents, their use is discouraged, and the researchers are attempting to investigate bioactive substances obtained from medicinal plants which might be used in the management of tumour and other deadly disorders (Coats 1994; LaPoint et al. 2011; Ashton 2012). Plants, which are the most significant source of therapeutic substances, have been gaining substantially more consideration of the analysts for their great viability and low poisonousness (Shah et al. 2015). Potato tumour measure has been directed on a few plants of different families with remarkable outcomes (Haque et al. 2000; Hussain et al. 2007). High anti-angiogenic action has likewise been shown by a few species of plants using chorioallantoic membrane (CAM) assay (MiuRA et al. 2002; Wang et al. 2004). Numerous bioactive substances obtained from different plants have been assessed against tumour, showing great potential (Da Rocha et al. 2001).

Sahreen et al. (2015) conducted a study in order to evaluate the anti-tumour and anti-antigenic activities of different extracts of *R. hastatus* using potato tumour assay. The results simplified that the methanolic extract showed effective anti-tumour potential followed by n-butanol, aqueous and chloroform. Further ethyl acetate and n-hexane fraction showed the least potential. The outcome of this study was found to be in accordance to other studies (Fatima et al. 2009) establishing that it is the concentration of the samples on which the tumour inhibition rates depend upon. Findings of the study confirmed the preceding reports of (Islam et al. 2010; Ashraf et al. 2015) confirming that the anti-tumour potential is attributed to the bioactive principles of the plant as well as their strong solubility with appropriate solvent and also proving the statement of (Fatima et al. 2009) that tumour induction was changeable in case of different extracts of solvent.

In another study performed by Ahmad et al. (2016a, b), the anti-tumour and anti-antigenic potential of crude saponins, methanol extract and various fractions of *R. hastatus* were evaluated**,** using potato tumour assay. The study found that the extracts exhibited notable potential in the assay. However the chloroform and saponin fractions exhibited the most prominent activities which lead to the conclusion that these might probably be potential targets for the isolation of bioactive compounds possessing anti-neoplastic action. It was noted that the anti-tumour activity possessed by some extracts of *R. hastatus* is more prominent than some

previously known instances from various plants (Haque et al. 2000; Hussain et al. 2007). Similarly, the anti-antigenic potential of the plant is comparable with different plants with strong antiangiogenic activities (Wang et al. 2004) as well as higher than the formerly reported daidzein and genistein (Krenn and Paper 2009). Furthermore it is evident from the above discourse that saponin and the chloroform extracts being the most active might be the potential sources of active compounds, which can strongly ameliorate metastasis and neo-vascularization.

6.8.8 Cytotoxic Activity

One of the most challenging diseases nowadays throughout the world is cancer which is one of the leading causes of mortality. A few variables have been accounted which cause hyperproliferation and malignancy (Borrego-Soto et al. 2015). The free radical-prompted lesions have been considered as one of the main sources of malignant growth (Valko et al. 2006). Different restorative systems are followed for the therapy of malignancy; however, chemotherapy has been considered as the most worthy and positive prognostic helpful methodology (Mohamed et al. 2015). Because of the useful and safe nature of all the medications from normal sources being biodegradable are favoured over the manufactured ones (Coats 1994). Different subsidiaries of natural anticancer medications are additionally being integrated and used against cancer (Jordan and Wilson 2004).

(Kamal et al. 2015) executed a study to establish the cytotoxic activity of crude saponins and methanolic extract as well as the subsequent fractions of *R. hastatus* against brine shrimps. Excellent activity was shown by the saponin extract at the concentration of 1000, 100 and 10 μg/mL. Among the fractions, the chloroform fraction also showed prominent cytotoxicity. However, ethyl acetate and crude methanol extract showed similar lethality as LC50 of 90 μg/mL. Further aqueous fraction and n-hexane fraction showed mediocre potential. The lethality caused in brine shrimps was notably highest in the case of the saponin extract, in which evidence is that anticancer properties might be attributed to these compounds. Moreover, it is also noted that the ethyl acetate and chloroform fraction showed remarkable cytotoxicity, which directs to the fact that the compounds (saponins and other components) responsible for the cytotoxicity are present in good amounts in these extracts. There is a positive correlation existing between the brine shrimp lethality assay and human nasopharyngeal carcinoma (KB cell line) as reported by Mclaughlin et al. (1998), Abdul et al. (2009), Fatima et al. (2009). All these results confirm the cytotoxic potential of different extracts of *R. hastatus.*

On the other hand, another study was conducted by Sahreen et al. (2015) to confirm the cytotoxic activities of *R. hastatus* roots, again using brine shrimp assay. Different fractions were evaluated for cytotoxicity, and the potential was found to be according to the following pattern: butanol > methanol > chloroform > aqueous > ethyl acetate > *n*-hexane. The earlier reports of (Hussain et al. 2010) were found in uniformity with the above findings, who also established that the methanol extracts

of *Rumex* species showed prominent cytotoxic potential and the plant was highly active against larvae of brine shrimp.

A more explained study was done by Ahmad et al. (2016a, b), to evaluate cytotoxic potential of this plant against NIH/3T3 and HeLa cell lines using different extracts of *R. hastatus*. It was aimed to find out the most active fraction of the plant, as well as the identification of bioactive constituents, causing cytotoxicity. It was found that all the solvent fractions were active against both cell lines but the chloroform fraction was prominent in activity against both cell lines. Furthermore the noted IC50 values along with the GC-MS analysis of chloroform fraction confirmed the presence of most of the active constituents in this fraction only, which also indicated the fact that this fraction should perhaps be the target for isolation of components useful in cytotoxic therapy to a large extent. The analysis of the chloroform extract also revealed some of the compounds possessing anticancer activities in *R. hastatus* including dihydrojasmone, phytol, anthracenedione, eicosanol, silane, aristolone, nonivamide, ar-tumerone, ethyl α-d-glucopyranoside and sitostenone. (Komiya et al. 1999), for instance, reported that, in human lymphoid leukaemia Molt 4B cells, phytol has been known to induce programmed cell death. Similarly (Flescher 2005) reported dihydrojasmone, a new family of anticancer agents, which is also one of the member of jasmonate family. In nanoparticle-type drug delivery system, silane has been confirmed as a remarkable agent, for anticancer compounds. Apart from anticancer activity, nonivamide a skin permeation enhancer used in various ointments etc. is also present in the chloroform fraction of the plant (Fang et al. 2001). Also, C20 aliphatic alcohols have been found useful in the management of hyperproliferative skin disorders, and eicosanol, present in *R. hastatus*, is also a C20 alcohol. Pope et al. (2001) and Firestone and Sundar (2009) also reported two sesquiterpenes, aristolone and Ar-tumerone, which show the cytotoxic potential. Similarly vitamin E, a phenolic compound with prominent free radical scavenging and cytotoxic activity, has also been reported (Baldioli et al. 1996; Yu et al. 2009; Salvador et al. 2013). The steroids extracted from plant extract were used against cancer cells. Therefore it shows that sitostenone, a natural steroid found in the plant extract after analysis, might also be responsible for the cytotoxic activity. Compiling all the results, it is very much evident that the chloroform fraction of *R. hastatus* possessed the most prominent activity against the two types of cell lines. Concluding from the above discourse, it's quite obvious that *R. hastatus* is a potent source of cytotoxic compounds, hence can be explored for the development of different drugs in this direction.

6.8.9 Antidiarrhoeal Activity

High death rate in developing nations is due to diarrhoea where more than 5,000,000 children under 5 die yearly from serious diarrhoeal infections (Heinrich et al. 2005). It is described by frequent recurrence of solid discharge, stomachache and wet stool (Maiti et al. 2007). Diarrhoeal ailment is a main source of mortality and bleakness, particularly in kids in developing nations (Mani et al. 2010). A dominant part of

diarrhoeal cases are because of bacterial enteropathogens, diarrhoeagenic *Escherichia coli* being the most widely recognized reason in developing nations. The traveller's diarrhoea is caused by two important bacterial classes of diarrhoeagenic *E. coli*, mostly enteroaggregative and enterotoxigenic (Adachi et al. 2001) and intrusive bacterial microorganisms like ***Campylobacter***, ***Shigella*** and ***Salmonella*** (Hoge et al. 1998). Thusly, there is a pressing requirement for the increase of research into plants claiming medicinal value in diarrhoeal infections (Mohammed et al. 2009). For the management of diarrhoeal infections, a large population of developing nations largely depend on natural medications. Considering this reality the World Health Organization has established a diarrhoeal disease control program, which incorporates investigations of conventional therapeutic practices, increasing health education and avoidance of the disease (Shaphiullah et al. 2003).

Very less research has been reported regarding the antidiarrhoeal activity of *R. hastatus*, though a study was undertaken by Shakuntala et al. (2011) to confirm the same using the ethanolic extract of the roots of *R. hastatus*. In normal gastrointestinal models of rats at 100, 150 and 200 mg/kg body weight, castor oil-induced diarrhoea was followed. The incidence, severity and the typical parameters of diarrhoea were reported to decrease with the increase in the doses of the ethanolic extract of the plant at 100, 150 and 200 mg/kg body weight. The prominent antimotility potential shown by the extract was comparable to the standard, atropine sulphate. This provides a basis to conclude that *R. hastatus* possesses some antidiarrhoeal potential, though more research and investigation are required in this direction.

6.8.10 Antimicrobial

Nowadays, most of the nations use plants as the main source of potent and effective drugs to treat various diseases and ailments (Srivastava et al. 1996). Different diseases and infections are treated by potent therapeutic agents isolated from plants (Uniyal et al. 2006). As an integrative system of medicine, plants are being accessed to confirm their antimicrobial potential for the management and protection against pathogens in recent years because the plant extracts possessing antimicrobial properties can be very vital. Potent natural compounds obtained from plants possess an important role in the defence mechanism of plants as well as their physiological actions in the human body (Sahreen et al. 2010). Resistance is the major drawback with the commercial antibiotics which are being used for various infections. Moreover, a bunch of toxic effects like hypersensitivity, immune suppression, etc. are connected with the use of these drugs. As a matter of fact, the plants are not only being widely used as drugs but as cosmetics and nutritional food as well, further evaluation of which by in vitro methods has confirmed their utility as antimicrobials and in other diseases as well (Krishnaiah et al. 2007).

Vast antimicrobial activity studies have been carried out on *R. hastatus*. In one of the study carried out by Sahreen et al. (2015) on methanol extract of the plant as well

as its different fractionated extracts, numerous plant extracts reflected prominent antimicrobial potential, which is why they are being widely used in PHCs. All these results show that the plant has immense potential for antimicrobial activity.

6.8.10.1 Antifungal

Sahreen et al. (2015) designed a study on *R. hastatus* roots using agar tube dilution method against *A. niger*, *A. flavus*, *A. fumigatus* and *F. solani*. Inhibition of all the fungi was observed which reflects the antifungal potential of *R. hastatus*, although it requires further research and investigation.

6.8.10.2 Antibacterial Activity

Diverse antibacterial studies have been conducted on *R. hastatus*. Sahreen et al. (2015) performed a study on different root extracts of *R. hastatus* using agar well diffusion method. Crude methanol extract was fractioned with n-hexane, chloroform, n-butanol, ethyl acetate and residual aqueous fraction. *Staphylococcus aureus* **which** is a Gram-positive bacteria was inhibited by the extracts in the following order chloroform>n-hexane>methanol; however the other extracts had no effect on the growth of the respective bacteria. Besides, the chloroform fraction followed by methanol, butanol and ethyl acetate inhibited *Bacillus subtilis*, although the rest of the extracts didn't inhibit the growth of the respective bacteria. Similarly, the Gram-negative bacteria *Klebsiella pneumonia***'s growth** was inhibited in the order, viz. ethyl acetate, n-hexane>methanol, whereas other fractions did not inhibit its growth. *Pseudomonas aeruginosa* was also found to be inhibited by the plant. Moreover, growth of *Salmonella typhi* was inhibited in the order n-hexane>n-butanol>ethyl acetate, chloroform, methanol and aqueous. Furthermore, the growth of *Enterobacter aerogenes* was inhibited in the order aqueous>methanol and chloroform, and the remaining fractions did not show inhibition of the respective bacteria. Additionally, *Micrococcus luteus* and *Escherichia coli* reflected no antibacterial activity of any of the extracts. All the above results strongly indicate very potent activity of *R. hastatus* against different Gram-positive and Gram-negative bacteria.

Similar findings were found in the study conducted by Andleeb et al. (2018). Under this research, analysis of antibacterial potential of *R. hastatus* against various clinical pathogenic bacteria such **as** *Serratia marcescens***,** *Escherichia coli***,** *Klebsiella pneumoniae***,** *Staphylococcus aureus***,** *Streptococcus pyogenes***,** *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* was performed using agar well diffusion method. The maximum inhibition of *S. pyogenes* was shown by the diethyl ether extract, while moderate inhibition was shown by chloroform fraction. Moderate inhibition of *K. pneumonia* and *S. aureus* was shown by diethyl ether and acetone fractions. Low or even no effect was shown by ethanol fraction on the growth of bacteria. Spot screening, TLC-bioautography and genomic DNA extraction (broth dilution method) also demonstrated the antibacterial effect of *R. hastatus*. Fine conclusion can be drawn from the above results that most of the extracts analysed were found to be promising source for the exploration of novel antimicrobials, thereby making it clear that *R. hastatus* could be successfully used as prominent antibacterial agent, as well as overcome the enigma of bacterial infections and

multidrug-resistant microbial strains. (Ogram et al. 1987) further analysed the effect of the plant extracts on microbial DNA extracted from sediments and drew the same conclusion (Sahreen et al. 2011). The fall in DNA damages was exhibited by different root extracts of the plant. Lastly further establishment of the activity was reflected by spot screening results which is in accordance with the studies of (Oke and Hamburger 2002; Hussain et al. 2010).

One more study was conducted by Kamal et al. (2015) in the same direction. The analysis of crude flavonoids, saponins, crude methanolic extract and resultant fractions of *R. hastatus* by well diffusion method was carried out. The flavonoid fraction showed potent activity against all strains, which was however followed by the saponin extract, comparable to the positive control in the antibacterial assay. Similarly good zones of inhibition were shown by the ethyl acetate and chloroform fractions; the largest was however displayed by flavonoid extract against *Bacillus cereus*, while saponin was more effective against *Escherichia coli*. All the extracts were effective against *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. Further analysis of various samples of *R. hastatus* revealed that this plant shows potent antibacterial activity; besides the flavonoid fraction was most active against different strains. It has already being established that this group of compounds is reported to possess remarkable anti-infective properties, and there are different compounds of flavonoids which have been discovered and identified, possessing potent antibacterial potential (Cushnie and Lamb 2005). Furthermore, it has been notified that synergistic effect is shown by numerous compounds of flavonoids when in combination, for instance, isorhamnetin-3-rutinoside, quercetin and rutin, present in the samples of *Marrubium globosum*, possess higher potential than the individual compound (Kimura and Yamada 1984). Moreover the saponins extracted from the plant also displayed prominent antibacterial potential against different bacterial strains which has also been reported by several investigators (Avato et al. 2006).

6.8.11 Antidiabetic Activity

Diabetes mellitus is a metabolic issue described by increment in blood glucose level. It can influence people at any phase of life, yet the recurrence of diabetes is extensively high among the corpulent and matured individuals (Mellitus 2005). Various restorative measures are utilized to reduce the indications of this ailment. One of the powerful helpful measures is to diminish the absorption of glucose from the digestive system. Hence, the retention of glucose from the digestive system can be diminished viably by α-glucosidase inhibition. Different plants have been accounted to have the α-glucosidase restraint potential (Ha et al. 2014). Diabetes mellitus is one of the regular metabolic issues with micro- and macrovascular complexities that cause noteworthy dismalness and death. It is considered as one of the five driving reasons for death on the planet (Vats et al. 2004; Kumar et al. 2006). In the present-day medication, no agreeable powerful treatment is as yet accessible to cure the disease (Ghosh and Suryawanshi 2001). There is expanding

request by patients to utilize natural compounds with antidiabetic potential because of reactions and after-effects related with the utilization of insulin and oral hypoglycaemic agents (Holman and Turner 1991; Kameswrarao et al. 1997; Rao et al. 2001). These constraints have generally incited the investigation of the executives systems including the utilization of plant-based drugs which are as well low-cost antidiabetic drugs with less announced toxic symptoms (Atanasov et al. 2015).

This research was designed by Ahmad et al. (2019) on the different samples of *R. hastatus* for exploration of its in vitro antidiabetic activity. Further analysis of the extracts through GC (FID-MS) confirmed the presence of 120 compounds, among which, few antidiabetic agents were also identified, viz. guanidine, phytol, caryophyllene, anozol, nerolidol, ethylthreonine, butyl phthalate, indoline, myristic acid, dihydrobenzofuran and palmitic acid. It is a clear indication that the plant possesses antidiabetic potential. It may also be concluded that *R. hastatus* is among low-risk and nutritious plants based on the reported data. It can therefore be labelled as green functional food with antidiabetic activity, along with the source of different secondary metabolites. Growth, energy production and other vital functions of the body can be thereby met effectively along with the possible management of diabetes mellitus. Furthermore, when the traditional vegetables are unavailable, scarce or highly priced, it can also be used in this direction as well.

6.9 Conclusion

The medicinal plants are highest source of different phytoconstituents, possessing diverse pharmacological and ethnomedicinal activities. Medicinal plants have various properties for curing of various diseases for so many years. Currently an extensive research is going on worldwide to find novel phytoconstituents possessing novel pharmacological activities. In this book chapter, the facts reported are hard to clearly establish the structure-activity relationships and functionality regarding the pharmacological effects of various phytoconstituents.

In this chapter the data are collected from all the sources regarding ethnomedicinal uses, botanical description, pharmacology and phytochemistry of *R. hastatus* (Polygonaceae) a healing herb wildly grown in the areas of southwest China, northern Pakistan and northeast Afghanistan. Various phytoconstituents like quinones, terpenoids, coumarins, flavonoids, volatile oil and carotenoids have been reported in *R. hastatus*. It is noteworthy that *R. hastatus* has extensive medicinal uses, as ethnobotanical and ethnomedicinal data indicate. It exhibits several pharmacological activities such anti-inflammatory, hepatoprotective, antidiabetic and anti-tumour. It is potentially an important medicinal plant for mankind. So well-designed clinical trials are needed in order to change from traditional to a well-established use of *R. hastatus* medicinal plant preparations for the prevention and treatment of various ailments.

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Chemical Composition and Biological Uses of *Crocus sativus* L. (Saffron)

7

Shruti Sharma and Dinesh Kumar

Abstract

Crocus sativus L. (Iridaceae) is a stemless herb produced in Iran, Afghanistan, Turkey, Spain, Greece, and India. It is commonly known as saffron and used since historical times as an important crop of food and nutraceuticals and for its therapeutic importance. The main use of this plant comes from yellow-coloured dried stigmas having a bitter taste and intense aroma. Saffron contains aroma-yielding compounds and volatiles (150) of different chemical natures such as terpenes, terpene alcohol, and their esters. Around 135 bioactive molecules have been isolated including chemical markers (crocin, crocetin, picrocrocin, and safranal) from *C. sativus*. The picrocrocin and safranal are major contributors for its bitter taste and hay fragrance. *Golden herb* possesses a variety of therapeutic potentials such as antimicrobial including antiparasitic and antibacterial, antioxidant, hypotensive, hypolipidemic, anxiolytic, antidepressant, anticonvulsant, antinociceptive, anti-inflammatory, diuretic, cytotoxic, etc. In addition, saffron also possesses various health-promoting properties like treating asthma, menstrual cramps, depression, and many more. Many ayurvedic and herbal formulations have been prepared from saffron which includes skincare and health-care products. Saffron is an expensive spice with a price of for 1 kg stigmas around 600–1000$. The high cost and demand of the golden spice encourage the scientific community to made efforts for its large-scale production. Hence, quality insurance of saffron needs to be certified as per ISO/FDA. The overview of the background, phytochemistry, pharmacological activities,

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substitutes, adulterants, toxicity, and formulations has been discussed along with quality and standardization methods of saffron.

Keywords

Crocus sativus · Iridaceae · Phytochemistry · Standardization · Saffron

Abbreviations

CIE	International Commission on Illumination
FDA	Food and Drug Administration
HPLC	High-performance liquid chromatography
MDA	Malondialdehyde
TLC	Thin layer chromatography

7.1 Introduction

Crocus sativus L. (Iridaceae) is a stemless high-value medicinal and aromatic plant found in Europe, Asia, and America. The saffron word originated from Safran, a French word that means "yellow" (Evans 1997; Harper 2001; Mozaffarian 1996). Etymologically, *Crocus* is derived from the Greek word *Croci* meaning thread and *Sativus* meaning cultivation (Deo 2003). The plant has different names region-wise, e.g. in Arab it is known as Zahafaran, and in India Saffron [Keshar (Hindi), Kumkuma (Sanskrit), and Kungumapu (Tamil)]. *C. sativus* in addition to dye, perfume, and medicine has also been considered in culinary since ages (Abrishami 1997). It is the world's most valuable spice because of short flowering season of fewer than 3 weeks and effortful harvesting and 1 kg of stigmas can cost up to 1000$ (USDA 2009). Saffron has a strong fragrance, bright yellow-orange colour, and bitter taste. For this reason, saffron is often used in the aroma as well as in colour industry (Wani et al. 2011; Saeidnia 2012).

7.2 Origin and History

Saffron has a historical background of use and cultivated since antiquity. It has been cultivated for use as a dye and was the most loved and high-value spice crop of ancient Greeks, Romans, and Egyptians. The evidences for the use of saffron are around from 2400 BC, and more proofs for its use in colouring tunics exist in Spain. The saffron became popular in Mesopotamia with the civilization of Babylonian culture. Ancient scripts talk about utilization as a flavouring agent during the rule of Hammurabi (1800–1700 BC) and are also found in the text of Kashmir (fifth century BC). Iran, India (J&K), and Spain are the highest growers of saffron in the global

Fig. 7.1 Pictorial representation of *Crocus sativus L. (saffron)*

market. In Persian text, the use of saffron for paper production as well as for the preparation of ink of different shades has been mentioned. Saffron ink was used to write the holy prayers and scripts by the rulers and royal peoples. There is also evidence of saffron use by Sumerians around 5000 years ago which signifies its silver past.

7.3 Morphology

Saffron is a perennial herb with purple-coloured flowers having three stamens and a corm of 2 in. diameter. Each corm produces 5–9 small leaves (Fig. 7.1). The plant propagates through corms by sprinkling the roots at the base and circumference of the corms. The flowering occurs in late winters and spring (Evans 1997). In the first year, the corms did not produce flower buds due to lack of proper nourishment. The flower contains three indistinguishable sepals and petals. From the centre of flowers is located an ovary which ends up in a yellow-coloured style that gives rise to orange-red coloured stigmas, the main source of saffron. Flowers are sterile and hence don't provide any seeds. Hence, the mode of propagation is through corms, and a single corm produces one to seven flowers (Srivastavan et al. 2010).

7.4 Classification

Kingdom—Plantae	**Family**—Iridaceae
Division—Magnoliophyta	**Species**—*sativus*
Class—Liliopsida	**Genus**—*Crocus*
Order—Asparagales	

7.5 Traditional Uses

Saffron has been used in European culinary since ages for colour and flavour and also as important ingredients of Gugelhupf which is a German cake. Additionally, dairy items incorporate it to impart colour and flavour. Romanians used saffron for relieving hangovers. It has excellent antispasmodic properties and is used for pain relief (sixteenth to nineteenth centuries; Schmidt and Betti 2007). It has expectorant, aphrodisiac, sedative, and anxiolytic effects. The Egyptian mentions saffron for kidney and liver problems and in dysentery, measles, gallbladder, and urinary tract infections (Baumann 1960; Grisolia 1974). However, a higher dosage of saffron may act as an abortifacient and also lead to temporary paralysis (Malairajan et al. 2006).

7.5.1 Phytochemistry of *C. sativus*

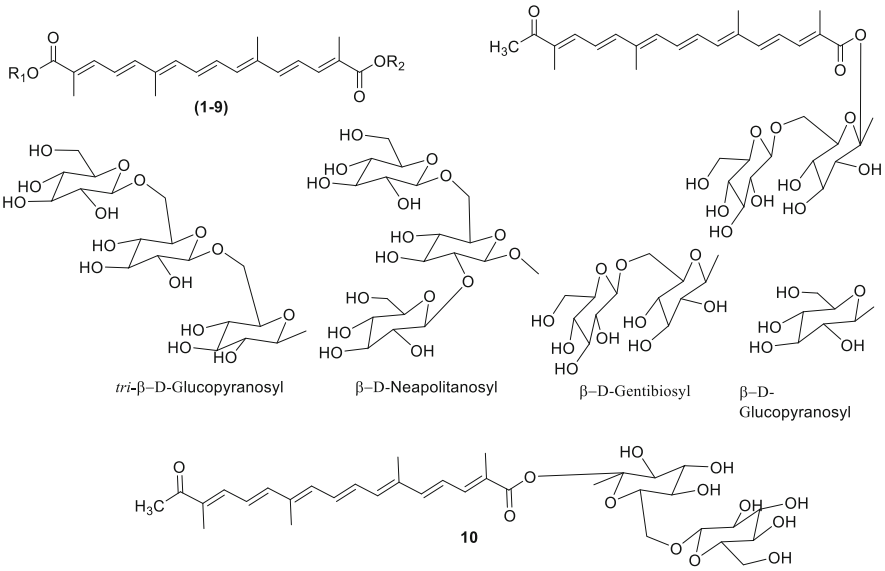
It is the most explored and well-known species of the genus *Crocus*. Crocetin and its esters, safranal and picrocrocin, are the quality control chemical markers of saffron. Major classes of compounds isolated from saffron include diterpenes, triterpenes, tetraterpenes, monoterpenoids, flavonoids and phenolics, carboxylic acids, sterols, nitrogen-containing compounds, and other classes. Detailed descriptions are discussed below.

7.5.1.1 Apocarotenoids and Their Derivative

It is the most characteristic class of phytochemicals that are reported in *C. sativus* stigmas. Crocetin (**1**) and its glycosidic esters crocins (**2–10**) are major water-soluble apocarotenoids, whereas phytoene, zeaxanthin, beta-carotene, and lycopene (**11–14**) are fat-soluble carotenoids present in saffron (Mykhailenko et al. 2019; García-Rodríguez et al. 2017; Figs. 7.2 and 7.3; Table 7.1). In saffron, the crocin is about 6–16% of dry weight and can further be increased to 30% by its cultivation and processing practices (Hu et al. 2015; Gregory et al. 2005; Kyriakoudi et al. 2012; Liorens et al. 2015). A novel xanthone, mangicrocin **(15)**, has also been reported from *C. sativus* stigmas (Ordoudi and Tsimidou 2004; Fig. 7.4).

7.5.1.2 Monoterpenoids

Picrocrocin (**16**) is a major chemical compound of volatile oil responsible for saffron essence, whereas safranal (**17**) constitutes over 60% of the oil and contributes to its bitter taste (Tarantilis and Polissiou 1997). Maggi and team provided the information that β-isophorone (**19**), isophorone isomer (**20**), α-pinene (**21**), 1,8-cineole (**22**), and β-ionone (**23**) are also the main components of essential oil, in addition to **16** and **17** (Maggi et al. 2010; Mykhailenko et al. 2019). (4*R*)-4-hydroxy-2,6,6-trimethylcyclohex-1-enecarbaldehyde4-O-[β-D-glucopyranosyl (1 → 3)-β-D-glucopyranoside] (**24**), a safranal glycoside, was reported from the alcoholic extract of saffron (Mykhailenko et al. 2019). Red saffron stigmas contain β-cyclocitral (**25**) and 4-oxoisophorone (**26**; Tarantilis and Polissiou 1997), whereas crocusatins (A-L; **27-38**) were isolated and reported from stigmas, petals, and pollens (Li and Wu



S.No	R1	R2
1.	H	H
2.	triglucocoside	gentiobioside
3.	nepolitanoside	gentiobioside
4.	gentiobioside	glucoside
5.	gentiobioside	gentiobioside
6.	gentiobioside	glucoside
7.	gentiobioside	H
8.	glucose	glucose
9.	glucose	H
10.	-	gentiobioside

Fig. 7.2 Diterpenes and triterpenes

2002a; Mykhailenko et al. 2019). The main monoterpenoids (**16-38**) from saffron are depicted in Fig. 7.5 and Table 7.1.

7.5.1.3 Flavonoids

Flavonoids are accumulated in all the tissues of *C. sativus*. The structure of flavonoids and their derivatives from *C. sativus* (compounds **39–89**) are depicted in Table 7.1 and graphed in Figs. 7.6, 7.7, 7.8, and 7.9. Flavonoids are further classified into different classes and discussed below in detail.

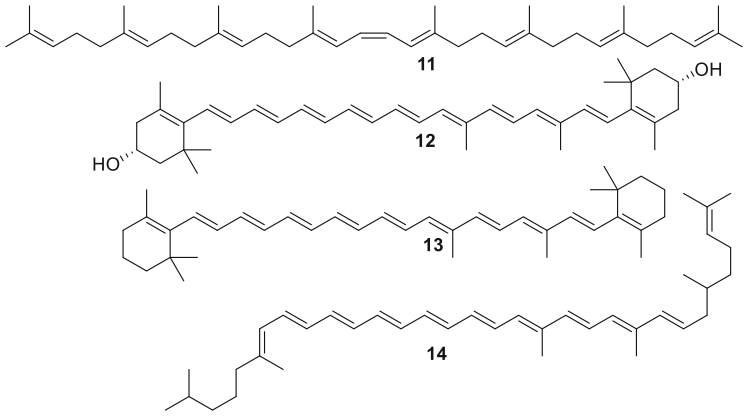


Fig. 7.3 Tetraterpenes

7.5.1.4 Flavone Derivatives

Flavones are the second most abundant class found in saffron. The compounds **39–70** fall under this category and are distributed in various tissues of the plant. The compounds are discussed in Table 7.1 and Fig. 7.6. The chromatographic studies based on mass fragmentation pattern detected the kaempferol (**39**), kaempferol 3-O-sophoroside-7-O-β-D-glucopyranoside (**40**), sophoraflavonoid (**41**), and kaempferol 7-O-β-D-sophoroside (**44**) in abundance (Mykhailenko et al. 2019) while kaempferol 3,7,4′-tri-O-β- glucopyranoside (**43**), kaempferol-3-dihexoside (**44**), astragalin (**45**; Li et al. 2004; Tung and Shoyama 2013), populin (**46**; Straubinger et al. 1997; Moraga et al. 2009a, 2009b), **47**, **48**, **49**, and their synthetically prepared derivatives such as **50 and 51** in low levels (Carmona et al. 2007;Vignolini et al. 2008; Montoro et al. 2008; Li et al. 2004). Similarly, quercetin, isorhamnetin, and their derivatives (**55–68**; Montoro et al. 2008, 2012; Norbeak et al. 2002), myricetin (**70**; Gismondi et al. 2012) and rhamnetin (**78**), were also reported in *C. sativus* stigmas (Fig. 7.6).

7.5.1.5 Flavonone Derivatives

Compounds (**71–75**) are categorized as flavonone derivatives and distributed in stigmas, petals, stamens, and leaves. The dihydrokaempferol (**71**; Mykhailenko et al. 2019), dihydrokaempferol 3-O-hexoside (**72**; Mykhailenko et al. 2019), and taxifolin 7-O-hexoside (**73**) were isolated, whereas naringenin 7-O-hexoside naringenin (**74–75)** were detected from stigmas **(**Mykhailenko et al. 2019; Fig. 7.7).

7.5.1.6 C-Flavone Derivatives

Compounds (**76–80**) are categorized as C-flavone derivatives and distributed mainly in leaves and tepals. Kaempferol 8-C-glycosides (**76-77**) were reported only in the leaves, whereas isoorientin (**78**), vitexin (**79**), and orientin (**80**) were noticed in the leaves and petals (Fig. 7.8; Mykhailenko et al. 2019).

Table 7.1 Phytochemicals from different parts of saffron

S. No	Identity	Part	References
Diterpenes and triterpenes			
1	Crocetin	Stigma; corms	Tarantilis and Polissiou (1997), Zhou et al. (2011)
2	*trans-/cis-crocetin* (tri-β-D-glucosyl)-(β-D-gentibiosyl) ester	Stigma	Zhou et al. (2011), Carmona et al. (2007)
3	*trans-/cis*-crocetin (β-D-neopolitanosyl)-(β-D-gentiobiosyl) ester	Stigma; flowers	Carmona et al. (2007)
4	*trans-/cis-crocetin* (β-D-neopolitanosyl)-(β-D-glucosyl) ester	Stigma	Carmona et al. 2007
5	*trans-/cis*-crocetin di-(β-D-gentiobiosyl) ester	Stigma; petals	Carmona et al. (2007), Pfander and Schurtenberge (1982), Straubinger et al. (1997)
6	*trans/cis*-crocetin (β-D-glucosyl)-(β-D-gentiobiosyl) ester)	Stigma; petals	Carmona et al. (2007), Montoro et al. (2012)
7	*trans/cis*-crocetin (β-D-gentiobiosil) ester	Stigma; petals	Pfander and Schurtenberger (1982), Montoro et al. (2012)
8	*trans/cis*-crocetin di-(β-D-glucosyl) ester	Stigma; petals	Pfander and Schurtenberger (1982), Carmona et al. (2007), Zhou et al. (2011)
9	*trans/cis*-crocetin (β-D-glucosyl) ester	Stigma; petals	Zhou et al. (2011)
10	*trans*-crocetin-1-al 1-O-β-D-gentiobiosyl ester	Stigma	Tung and Shoyama (2013)
Tetraterpenes			
11	Phytoene	Stigma	Grosso (2016)
12	Zeaxanthin	Stigma	Grosso (2016), Pfander and Schurtenberger (1982)
13	β-Carotene	Stigma	Grosso (2016), Pfander and Schurtenberger (1982)
14	Lycopene	Stigma	Grosso (2016), Pfander and Schurtenberger (1982)
Xanthone-carotenoid glycosidic conjugate			
15	Mangicrocin	Stigma	Ordoudi and Tsimidou (2004)
Monoterpenoids			
16	Picrocrocin	Stigma; petals	Zhou et al. (2011), Moraga et al. (2009a, b), Montoro et al. (2012)
17	Safranal	Stigma; flowers	Tarantilis and Polissiou (1997)
18	Safranal isomer	Stigma	Tarantilis and Polissiou (1997)
19	β-Isophorone	Stigma	Lage et al. (2015)
20	Isophorone isomer	Stigma	Tarantilis and Polissiou (1997)
21	α-Pinene	Stigma	Lage et al. (2015)
22	1,8-Cineole	Stigma	Lage et al. (2015)
23	β-Ionone	Stigma	Lage et al. (2015)

(continued)

Table 7.1 (continued)

S. No	Identity	Part	References
24	(4*R*)-4-Hydroxy-2,6,6-trimethylcyclohex-1-enecarbaldehyde 4-O-[β-D-glucopyranosyl(1 → 3)-β-D-glucopyranoside]	Stigma	Tung and Shoyama, (2013)
25	β-Cyclocitral	Stigma	Moraga et al. (2009a, b), Montoro et al. (2012), Lage et al. (2015)
26	4-Oxoisophorone	Stigma	Lage et al. (2015)
27	Crocusatin A	Pollen	Li and Wu (2002a)
28	Crocusatin B	Pollen	Li and Wu (2002a)
29	Crocusatin C	Stigma; petals; pollen	Li and Wu (2002a)
30	Crocusatin D	Petals; pollen	Li and Wu (2002a)
31	Crocusatin E	Stigma; pollen	Li and Wu (2002a)
32	Crocusatin F	Stigma; pollen	Li and Wu (2002a)
33	Crocusatin G	Stigma	Li and Wu (2002a)
34	Crocusatin H	Stigma	Li and Wu (2002a)
35	Crocusatin I	Petals	Li et al. (2004)
36	Crocusatin J	Stigma; petals	Li and Wu (2002a)
37	Crocusatin K	Petals	Li et al. (2004)
38	Crocusatin L	Petals	Li et al. (2004)
Flavonoids			
Flavon derivatives			
39	Kaempferol	Stigma; petals	Li et al. (2004), Montoro et al. (2012), Gismondi et al. (2012)
40	Kaempferol 3-O-sophoroside-7-O-β-D-glucopyranoside	Stigma	Straubinger et al. (1997), Carmona et al. (2007), Vignolini et al. (2008)
41	Sophoraflavonolosid (kaempferol-3-O-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranoside; kaempferol-3-O-β-D-sophoroside)	Stigma; tepals; pollen; leaves	Carmona et al. (2007), Vignolini et al. (2008), Moraga et al. (2009a, b)
42	Kaempferol 7-O-β-D-sophoroside	Stigma	García-Rodríguez. et al. (2017)
43	Kaempferol 3,7,4′-tri-O-β-glucopyranoside	Stigma	Carmona et al. (2007), Vignolini et al. (2008), Moraga et al. (2009a, b)
44	Kaempferol-3-dihexoside	Stigma	Carmona et al. (2007)
45	Astragalin	Stigma; petals	Li et al. (2004), Tung and Shoyama (2013)

(continued)

Table 7.1 (continued)

S. No	Identity	Part	References
46	Populin	Stigma; petals	Montoro et al. (2008), Straubinger et al. (1997)
47	Kaempferol 3-O-β-D-glucopyranosyl-(1 → 2)-O-β-D-glucopyranosid-7-O-β-D-glucopyranoside	Stigma	Li et al. (2004)
48	Kaempferol 3-O-α-L-(2-O-β-D-glucopyranosyl)rhamnopyranoside-7-O-β-D-glucopyranoside	Stigma	Li et al. (2004)
49	Kaempferol 3-O-β-D-(2-O-β-D-glucopyranosyl)glucopyranoside	Petals	Li et al. (2004), Montoro et al. (2012)
50	Kaempferol 3-O-β-D-(2-O-β-D-6-O-acetylglucosyl)glucopyranoside	Stigma; petals	Montoro et al. (2008), Li et al. (2004)
51	Kaempferol 3-O-α-L-(2-O-β-D-glucopyranosyl)rhamnoperanoside-7-O-β-D-(6-O-acetyl) glucopyranoside	Stigma	Li et al. (2004)
52	Kaempferol 3,7-di-O-β-D-glucopyranoside	Pollen; petals; stamens	Li et al. (2004), Montoro et al. (2012), Li and Wu (2002a)
53	Kaempferol 3-O-α-L-(2-O-β-D-glucopyranosyl)rhamnopyranosides	Tepals	Sánchez-Vioque et al. (2016)
54	Kaempferol 3-O-β-D-sophoroside-7-O-α-L-rhamnopyranoside	Tepals	Sánchez-Vioque et al. (2016)
55	Quercetin	Stigma	Li et al. (2004), Gismondi et al. (2012)
56	Helichrysoside	Tepals	Ordoudi and Tsimidou (2004), Zhou et al. (2011)
57	Tamarixetin 3-O-bihexoside	Sepals; stamens	Montoro et al. (2012)
58	Quercetin 3,4′-di-O-β-D-glucopyranoside	Tepals	Sánchez-Vioque et al. (2016)
59	Quercetin-3,7-di-O-β-D-glucopyranoside	Petals; stamens; flowers	Montoro et al. (2012)
60	Quercetin 3-O-β-D-sophoroside	Tepals	Montoro et al. (2012)
61	Quercetin 3-O-β-D-glucopyranoside	Stamens; petals	Montoro et al. (2012)
62	Quercetin 3-O-β-D-glucopyranosyl-(1 →2)-*α*-L-rhamnopyranoside-7-O-β-D-glucopyranoside	Flowers	Sánchez-Vioque et al. (2016)
63	Rhamnetin	Stamens; petals	Montoro et al. (2012), Termentzi and Kokkalou (2008)
64	Isorhamnetin	Petals	Montoro et al. (2012)
65	Crosatoside A	Pollen	Montoro et al. (2012)

(continued)

Table 7.1 (continued)

S. No	Identity	Part	References
66	Isorhamnetin 3,4′-di-O-β-D-glucopyranoside	Pollen; petals	Li and Wu (2002b), Montoro et al. (2008)
67	Isorhamnetin 3,7-di-O-β-D-glucopyranoside	Stamens; petals	Montoro et al. (2012)
68	Isorhamnetin-3-O-β-D-glucopyranoside	Pollen ; stigma; stamens; petals	Montoro et al. (2012); Li and Wu (2002b), Baba et al. (2015a, b)
69	Isorhamnetin-3-O-robinobioside	Pollen	Li and Wu (2002b)
70	Myricetin	Stigma	Gismondi et al. (2012)
Flavonon derivatives			
71	Dihydrokaempferol 7-O-β-D-glucopyranoside	Stigma	García-Rodríguez. et al. (2017)
72	Dihydrokaempferol 3-O-hexoside	Stigma; petals	Baba et al. (2015a, b), Montoro et al. (2008)
73	Taxifolin 7-O-hexoside	Stigma; petals; stamens	Baba et al. (2015a, b), Montoro et al. (2008, 2012)
74	Narinrenin 7-O-hexoside	Petals	Montoro et al. (2008)
75	Naringenin	Petals; stamens; leaves	Termentzi and Kokkalou (2008), Montoro et al. (2012), Baba et al. (2015a, b)
C-flavon derivatives			
76	Kaempferol-8-C-β-D-glycopyranosyl-6,3-di-O-β-D-glucopyranoside	Leaves	Sánchez-Vioque et al. (2016)
78	Isoorientin	Tepals	
79	Vitexin	Tepals; leaves	
80	Orientin	Tepals; leaves	
Anthocyanin			
81	Delphinidin 3,7-di-O-β-glucopyranoside	Petals	Lotfi et al. (2015), Nørbæk et al. (2002)
82	Petunidin 3,5-di-O-β-D-glucopyranoside	Tepals	
83	Petunidin 3,7-di-O-β-glucopyranoside	Tepals	
84	Petunidin 3-O-β-D-glucopyranoside	Tepals	
85	Myrtillin	Tepals	
86	Petunidin	Tepals	
87	Callistephin	Tepals	
88	Pelargonin	Tepals	
89	Cyanin	Tepals	

(continued)

Table 7.1 (continued)

S. No	Identity	Part	References
Phenols and phenol carboxylic acids			
90	Caffeic acid	Stigma; corms	Gismondi et al. (2012)
91	Chlorogenic acid	Stigma	Gismondi et al. (2012)
92	Ferulic acid	Corms	Esmaeili et al. (2011)
93	*p*-Coumaric acid	Corms; petals	Esmaeili et al. (2011)
94	Sinapic acid	Corms; petals	Termentzi and Kokkalou (2008), Baba et al. (2015a, b)
95	Gallic acid	Stigma; corms	Gismondi et al. (2012)
96	Protocatechuic acid	Petals	Li et al. (2004)
97	Vanillic acid	Petals	Li et al. (2004)
98	*p*-Hydroxybenzoic acid	Corms; petals; pollens	Li et al. (2004); Esmaeili et al. (2011)
99	3-Hydroxy-4-methoxybenzoic acid	Petals	Li et al. (2004)
100	Syringic acid	Corms	Esmaeili et al. (2011)
101	Gentisic acid	Corms	Esmaeili et al. (2011)
102	Salicylic acid	Corms	Esmaeili et al. (2011)
103	Benzoic acid	Pollen	Li and Wu (2002b)
104	Cinnamic acid	Corms	Esmaeili et al. (2011)
105	Protocatechuic acid methyl ester	Petals; pollen	Li et al. (2004)
106	Methylparaben	Petals; pollen; stigma	Li et al. (2004), Li and Wu (2002a, b)
107	(3*S*),4-Dihydroxybutyric acid	Petals	Li et al. (2004)
Phytosterols			
108	β-Sitosterol	Stigma; corms; flowers; pollen	Feizy and Reyhani (2016)
109	Stigmasterol	Stigmas; corms; flowers; stamens	Feizy and Reyhani (2016)
110	Fagasterol	Flowers	Feizy and Reyhani (2016)
111	Fucosterol	Flowers	Feizy and Reyhani (2016)
112	Campesterol	Corms	Feizy and Reyhani (2016)
Vitamins			
113	Riboflavin	Stigma	Lim (2014)
114	Thiamine	Stigma	Lim (2014)
115	Piridoxal	Stigma	Lim (2014)

(continued)

Table 7.1 (continued)

S. No	Identity	Part	References
Nitrogen-containing compounds			
116	Tribulusterine	Petals; stigma	Li et al. (2004), Li and Wu (2002a), Termentzi and Kokkalou (2008)
117	Adenosine	Petals; pollen; stigma; sprouts	Li et al. (2004), Li and Wu (2002a), Termentzi and Kokkalou (2008)
118	Harman	Petals; stigma	Li et al. (2004), Li and Wu (2002a)
119	Nicotinamide	Petals; pollen; stigma	Li et al. (2004), Li and Wu (2002a)
120	Uracil	Pollen; stigma	Li and Wu (2002a, b)
121	Thymine	Pollen; stigma	Li and Wu (2002a, b)
Furan derivatives			
122	(4*R*)-4-Hydroxy-dihydrofuran-2-one-O-β-D-glucopyranoside	Stigma	Li and Wu (2002a, b)
123	(4*S*)-4-Hydroxy-dihydrofuran-2-one-O-β-D-glucopyranoside	Stigma	Li and Wu (2002a, b)
124	2-Formyl-5-methoxyfuran	Stigma	Li and Wu (2002a 2002b)
Triterpenoid saponins			
125	Azafrin 1	Corms	Rubio-Moraga et al. (2011)
126	Azafrin 2	Corms	Rubio-Moraga et al. (2011)
Acetophenones			
127	2,3,4-Trihydroxy-6-methoxyacetophenone-3-O-β-D-glucopyranoside	Sprouts	Gao et al. (1999a)
128	2,4-Dihydroxy-6-methoxyacetophenone-2-O-β-D-glucopyranoside	Sprouts	Gao et al. (1999a)
Anthraquinones			
129	Emodin	Sprouts	Gao et al. (1999b)
130	2-Hydroxyemodin	Sprouts	Gao et al. (1999b)
131	1-Methyl-3-methoxy-8-hydroxyanthraquinone-2-carboxylic acid	Sprouts	Gao et al. (1999b)
132	1-Methyl-3-methoxy-6,8-dihydroxyanthraquinone-2-carboxylic acid	Sprouts	Gao et al. (1999b)
Others			
133	Crosatoside B β-(phydroxyphenyl)ethanol-α-O-L-rhamnopyranosyl (1 → 2)-β-D-glucopyranoside	Pollen	Li and Wu (2002a)

(continued)

Table 7.1 (continued)

S. No	Identity	Part	References
134	Sodium(2*S*)-(O-hydroxyphenyl) lactate	Stigma	Li and Wu (2002a)
135	3-(*S*)-3-β-D-glucopyranosyloxybutanolide	Sprouts	Gao et al. (1999a)

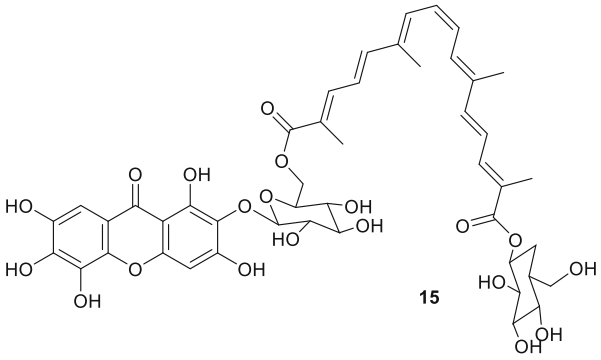


Fig. 7.4 Xanthones

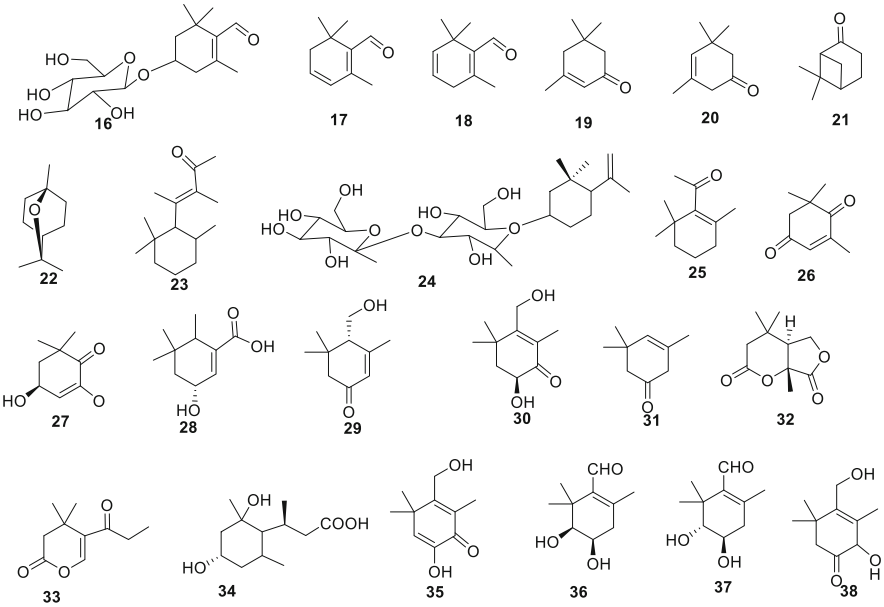
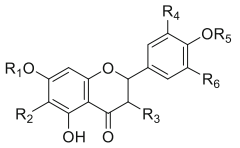


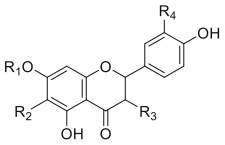
Fig. 7.5 Monoterpenoids and cyclohexane/hexene derivatives



(39-70)

	OR_1	R_2	R_3	R_4	OR_5	R_6
39.	H	H	OH	H	OH	H
40.	*β*-Glc	H	*O*-*β*-Glc-1 → 2-O-*β*-Glc	H	OH	H
41.	OH	H	*O*-*β*-Glc-1 → 2-*β*-Glc	H	OH	H
42.	*β*-Glc-1 → 2-*β*-Glc	H	OH	H	OH	H
43.	*O*-*β*-Glc	H	*O*-*β*-Glc	H	*O*-*β*-Glc	H
44.	H	H	O-hex-hex	H	OH	H
45.	H	H	*O*-*β*-Glc	H	OH	H
46.	*β*-Glc	H	OH	H	OH	H
47.	*β*-Glc	H	*O*-*β*-Glc-1 → 2-O-*β*-Glc	H	OH	H
48.	*β*-Glc	H	O-*α*-(2-O-*β*-Glc-Rha)	H	OH	H
49.	H	H	*O*-*β*-Glc-(2-O-*β*-Glc)	H	OH	H
50.	H	H	*O*-*β*-Glc-(2-O-*β*-acetyl)	H	OH	H
51.	*β*-(6-O-acetyl-Glc)	H	O-*α*-(2-O-*β*-Glu-Rha)	H	OH	H
52.	*β*-Glc	H	*O*-*β*-Glc	H	OH	H
53.	H	H	O-*α*-(2-O-*β*-Glu-Rha)	H	OH	H
54.	*α*-Rha	H	*O*-*β*-Glc-1 → 2-*β*-Glc	H	OH	H
55.	H	H	OH	OH	OH	H
56.	H	H	O-*p*-coumaroyl-Glc	OH	OH	H
57.	H	H	O-hex-hex	OH	OCH_3	H
58.	H	H	*O*-*β*-Glc	OH	*O*-*β*-Glc	H
59.	*β*-Glc	H	*O*-*β*-Glc	OH	OH	H
60.	H	H	*O*-*β*-Glc-1 → 2-O-*β*-Glc	OH	OH	H
61.	H	H	*O*-*β*-Glc	OH	OH	H
62.	*β*-Glc	H	*O*-*β*-Glc-1 → 2-O-*α*-Rha	OH	OH	H
63.	CH_3	H	OH	OH	OH	H
64.	H	H	OH	OCH_3	OH	H
65.	H	H	OH	OCH_3	*O*-*α*-Rha-(1→)-*β*-Glu	H
66.	H	H	*O*-*β*-Glc	OCH_3	*O*-*β*-Glc	H
67.	Glc	H	*O*-*β*-Glc	OCH_3	OH	H
68.	H	H	*O*-*β*-Glu	OCH_3	OH	H
69.	H	H	*O*-*β*-Rob	OCH_3	OH	H
70.	H	H	OH	OH	OH	OH

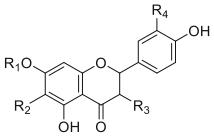
Fig. 7.6 Flavone derivatives



(71-75)

	R1	R2	R3	R4
71.	*β*-D-Glc	OH	OH	H
72.	H	OH	O-hex	H
73.	H	OH	O-hex	OH
74.	hex	OH	H	H
75.	H	OH	H	H

Fig. 7.7 Flavanone derivatives



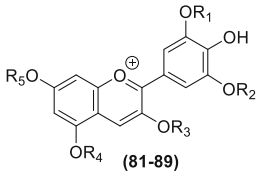
(76-80)

	R1	R2	R3	R4
76.	*C*-*β*-Glc	*O*-*β*-Glc	*O*-*β*-Glc	H
77.	*C*-*β*-Glc	*O*-*β*-Glc	OH	H
78.	H	*C*-*β*-Glc	H	OH
79.	*C*-*β*-Glc	H	H	H
80.	*C*-*β*-Glc	H	H	OH

Fig. 7.8 *C*-flavone derivatives

7.5.1.7 Anthocyanins

Compounds (**81–89**) are categorized as anthocyanins and distributed mainly in tepals and petals of violet saffron (Lotfi et al. 2015). Nine anthocyanin derivatives, namely, 3,7-di-O-β-glucoside of delphinidin (**81**) and petunidin (**83**), 3,5-di-O-β-glucoside of petunidin (**82**), 3-O-β-D-glucosides of petunidin (**84**) and delphinidin (**85**), petunidin (**86**), pelargonidin 3-O-β-D-glycopyranoside (**87**), pelargonidin 3,5-glycosides (**88**), and 3,5 cyanidin-diglycoside (**89**) were identified using HPLC (Fig. 7.9; Norbeak et al. 2002).



(81-89)

	R1	R2	R3	R4	R5
81.	H	H	*β*-glucoside	*H*	*β*-glucoside
82.	CH_3	H	*β*-glucoside	*β*-glucoside	H
83.	CH_3	H	*β*-glucoside	*H*	*β*-glucoside
84.	H	CH_3	*β*-glucoside	H	H
85.	H	H	*β*-glucoside	H	H
86.	H	CH_3	H	H	H
87.	-	-	*β*-glucoside	H	H
88.	-	-	*β*-glucoside	*β*-glucoside	H
89.	*H*	-	*β*-glucoside	*β*-glucoside	H

Fig. 7.9 Anthocyanins

7.5.1.8 Phenols and Their Derivatives

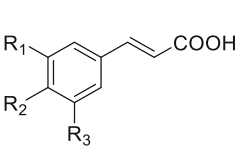
Stigmas of *C. sativus* were studied in-depth for its aromatic compounds (**90-107**). The distribution of these compounds among the different tissues was categorized under this class. The hydroxycinnamic acids, caffeic acid (**90**), chlorogenic acid (**91**; Gismondi et al. 2012), ferulic acid (**92**), *p*-coumaric acid (**93**), and sinapic acid (**94**), were reported in *C. sativus*. (Fig. 7.10 and Table 7.1). Several isolated and identified hydroxybenzoic acids and carboxylic acid, namely, gallic acid (**95**; Mykhailenko et al. 2019), protocatechuic acid(**96**), vanillic acid (**97**), *p*-hydroxybenzoic acid (**98**), 3-hydroxy-4-methoxybenzoic acid (**99**), syringic acid (**100**), gentisic acid (**101**), salicylic acid (**102**), benzoic acid (**103**), cinnamic acid (**104**), protocatechuic acid methyl ester (**105**), methylparaben (**106**; Li and Wu 2002a), and (3*S*),4-dihydroxybutyric acid (**107**), were reported (Fig. 7.10).

7.5.1.9 Phytosterols

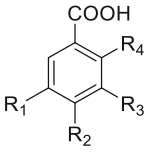
Phytosterols (**108–112**) were detected in stigma, petals, and corms (Feizy and Reyhani 2016; Fig. 7.11 and Table 7.1).

7.5.1.10 Vitamins

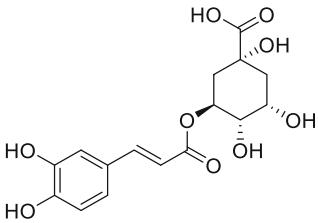
Three vitamins, namely, riboflavin (**113**; Hashemi and Erim 2016), thiamine (**114**), and pyridoxal (**115**; Lim 2014), were detected in stigma.



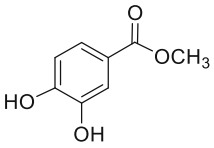
(90-94)



(95-103)



104



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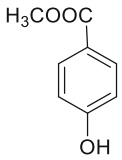
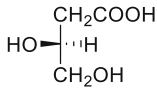


106



107

	R1	R2	R3	R4
90.	OH	OH	H	
91.	H	H	H	
92.	OCH_3	OH	H	
93.	H	OH	H	
94.	OCH_3	H	H	
95.	OH	OH	OH	H
96.	H	OH	OH	H
97.	H	OH	OCH_3	H
98.	H	OH	H	H
99.	H	OCH_3	OH	H
100.	OCH_3	OH	OCH_3	H
101.	OH	H	H	OH
102.	H	H	H	OH
103.	H	H	H	

Fig. 7.10 Phenolics and carboxylic acids

7.5.1.11 Nitrogen-Containing Compounds

Tribusterine (**116**), adenosine (**117**), harman (**118**), nicotinamide (**119**), uracil (**120**), and thymine (**121**; Fig. 7.12) were detected in stigmas, petals, sprouts, and pollens (b; Li and Wu 2002a).

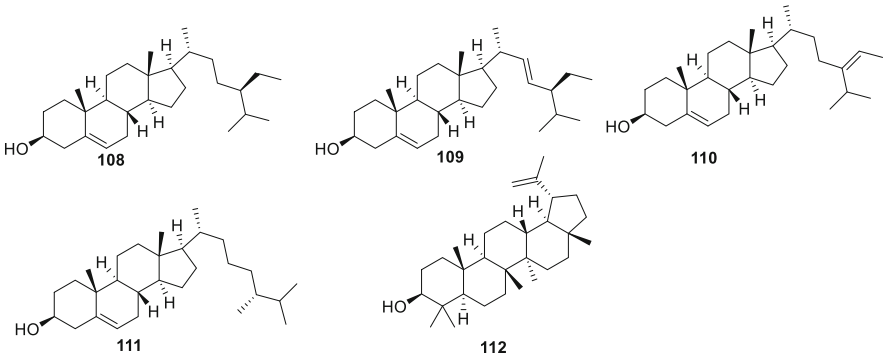


Fig. 7.11 Phytosterols

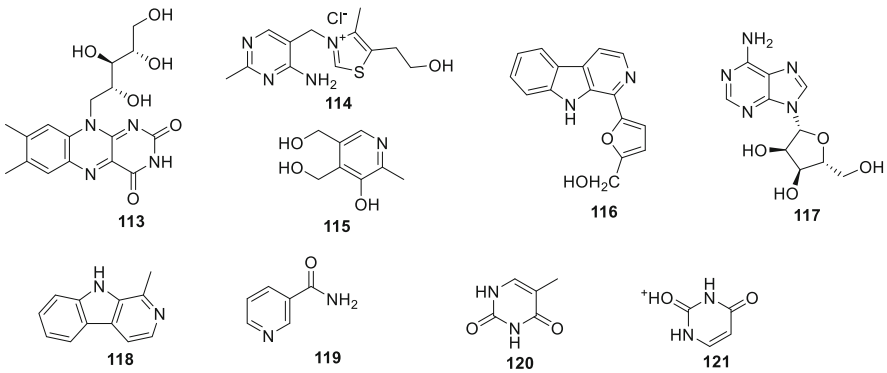


Fig. 7.12 Nitrogen containing compounds

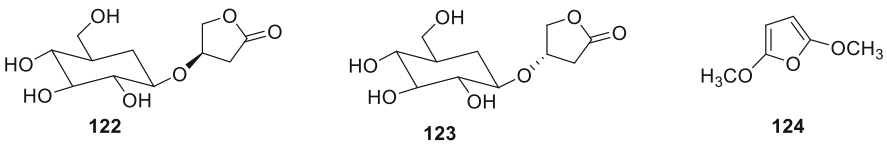


Fig. 7.13 Furans

7.5.1.12 Furan Derivatives

(4*R*)-4-Hydroxy-dihydrofuran-2-one-O-β-D-glucopyranoside (**122**), (4*S*)-4-hydroxy-dihydrofuran-2-one-O-β-D-glucopyranoside (**123**), and 2-Formyl-5-methoxyfuran (**124**) were detected in stigmas (Fig. 7.13; Li and Wu 2002a, b).

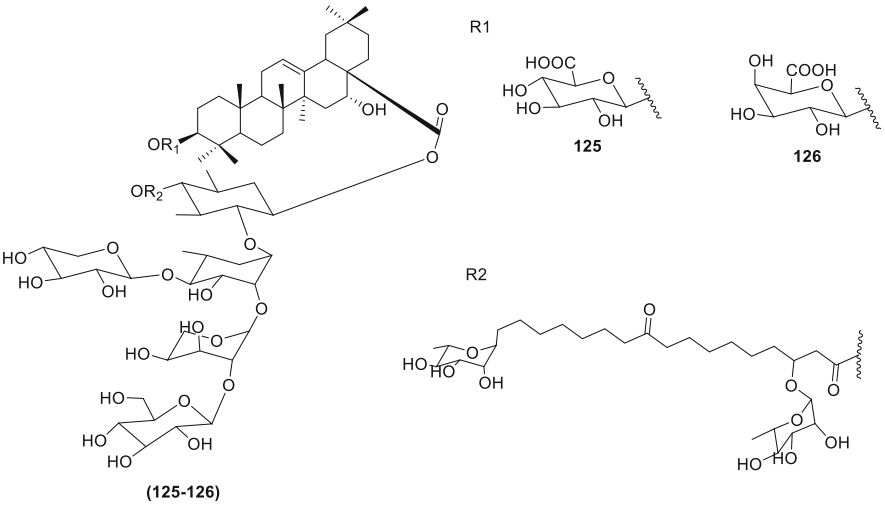


Fig. 7.14 Triterpenoid saponin

7.5.1.13 Triterpenoid Saponins

Two saponins, namely, azafrine1 (**125**) and azafrine2 (**126**), were reported from corms of saffron (Fig. 7.14; Mykhailenko et al. 2019).

7.5.1.14 Acetophenones and Anthraquinones

Acetophenones such as 2,3,4-trihydroxy-6-methoxyacetophenone-3-β-D-glucopyranoside (**127**) and 2,4-dihydroxy-6-methoxyacetophenone-2-β-D-glucopyranoside (**128**) and anthraquinones like emodin (**129**), 2-hydroxyemodin (**130**), 1-methyl-3-methoxy-8-hydroxyanthraquinone-2-carboxylic acid (**131**), and 1-methyl-3-methoxy-6,8-dihydroxyan- thraquinone-2-carboxylic acid (**132**) were isolated sprouts of *C. sativus* (Fig. 7.15; Gao et al. 1999a, b).

7.5.1.15 Others

γ-Lactone type of glucoside [3-(*S*)-3-β-D-glucopyranosyloxybutanolide] was isolated and characterized from sprouts of saffron (Gao et al. 1999a). Furthermore, macro- and micronutrients (Fe, Cu, Mn, Zn, Ca; Mykhailenko et al. 2019), amino acids, and saturated fatty acids were also detected in saffron (Table 7.1; Lim 2014; USDA 2013).

7.5.2 Pharmacological Activities

7.5.2.1 Antiparasitic and Antibacterial Activity

Several studies are reported on *C. sativus* for these activities. The isolated compounds from saffron (safranal and crocin) and semi-synthetic safranal derivatives were assessed against *Helicobacter pylori* for antibacterial and

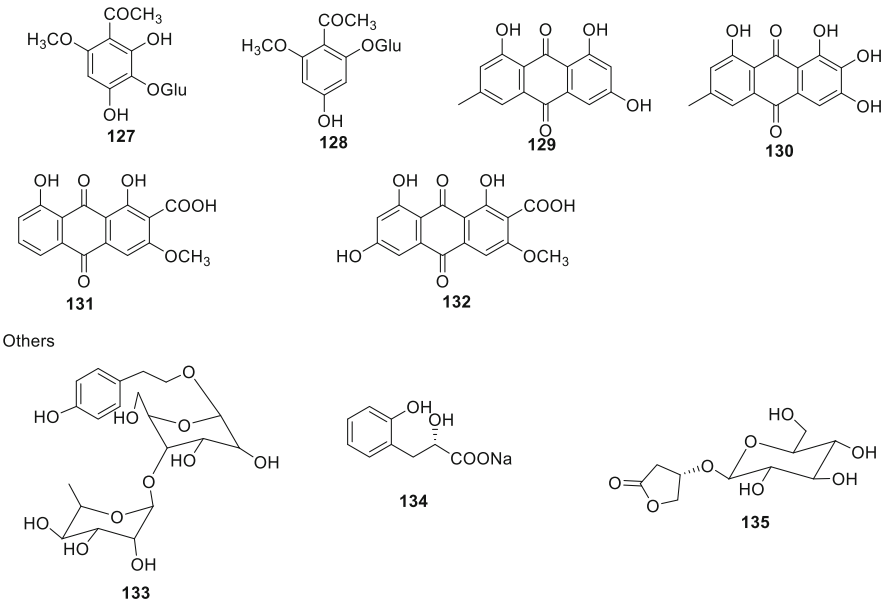


Fig. 7.15 Acetophenones and anthraquinones

plasmodia and leishmania for antiparasitic potential, respectively (De Monte et al. 2015). The MIC_{50} of safranal against *H. pylori* was observed at 32.0 μg/mL, while its two synthetic derivatives (thiosemicarbazonic) at 4–8 μg/mL, exceeding the values of reference drugs metronidazole and clarithromycin (>32 μg/mL). Hydrazothiazole was the most active compound (2–4 μg/mL). The synthetic derivatives showed lower activity against malaria, but high antileishmanial potential against *L. infantum* and *L. tropica* (IC_{50}, 6–16 μg/mL) was observed when compared to amphotericin B antibiotic (IC_{50}, 0.07–0.11 μg/mL). The highest antimalarial potential of crocin (IC_{50}, 18.93 μg/mL) and safranal (IC_{50}, 20 μg/mL) was found against the sensitive strain of chloroquine. Later, in vivo antimalarial activity of saffron stigmas was carried out against *Plasmodium berghei*. Chloroquine was used as a reference standard for accessing water and ethyl acetate extracts. The extracts moderately suppressed the parasitic count, but the combination of ethyl acetate fraction and chloroquine showed enhanced activity which further increases the survival percent of the mice as compared to treated with individual drug (Pestechian et al. 2015). Saffron leaves do not have any antimicrobial activity, while petals showed the activity against *S. aureus*, *S. enteric*, and *S. dysenteriae* (Jadouali et al. 2019).

7.5.2.2 Antioxidant Activity

Phenolics, crocetin, crocin, and safranal exhibited antioxidant activity in free radical scavenging assay (Hu et al. 2015). Saffron extract (300 μg/mL) showed 68.2% and 78.9% inhibition in the scavenging and reducing assays, respectively (Karimi et al.

2010). *C. sativus* leaves, petals, and flowers were also assessed for the concentration-dependent antioxidant potential, whereas petals showed highest while leaves were negligible in activities. Further, β-carotene oxidation inhibition and Cu^{2+}-chelating capacity determined the antioxidant potential of leaves, tepals, and corms of saffron. The finding indicated that tepals and leaves reduced the oxidation of β-carotene, while corms were found as poor antioxidant with slight Cu^{2+}chelating potential (Mykhailenko et al. 2019).

7.5.2.3 Hypotensive Activity

The hydro-alcoholic extract (200 mg/kg) of saffron stigmas were studied in normotensive and L-NAME-induced hypertensive rats (Nasiri et al. 2015), and it was observed that extract prohibited the rise in blood pressure and aortic reconstruction ($^*P < 0.001$). In another study, intravenous administration of safranal (1 mg/kg) and crocin (200 mg/kg) caused the reduction in the mean arterial blood pressure of the rats (60 ± 8.7, 50 ± 5.2, and 51 ± 3.8 mmHg, respectively) (Imenshahidi et al. 2010). Thus, both molecules of saffron showed excellent potential to treat hypertension.

7.5.2.4 Antidepressant Activity

Both stigmas and corms of the saffron have antidepressant potential that may be attributed due to the presence of crocin (Wang et al. 2010). Moreover, the saffron petals showed moderate activity at a dose of 30 mg/day (Moshiri et al. 2006).

7.5.2.5 Anxiolytic

Crocin was evaluated to assess its role to produce anxiolytic effects in light/dark model of rodents. The crocins (50 mg/kg) and diazepam (1.5 mg/kg) showed increase in latency time to enter the dark area and increased the time spent in the light compartment, while lower doses of crocins (15–30 mg/kg) did not modify the animal's behaviour. These findings clearly indicated the anxiolytic potential of crocin (Pitsikas et al. 2008).

7.5.2.6 Anticonvulsant

The anticonvulsant potential of saffron (safranal and *crocin)* was investigated in pentylenetetrazol-induced epileptic model of rodents. The safranal at a dose of 0.15 and 0.35 ml/kg body weight, *i.p.*, reduced the time interval of seizure, delayed onset of tonic seizures, and also protected the mice from death, while crocin (22 mg/kg, i.p.) did not show any antiepileptic activity (Hosseinzadeh and Talebzadeh 2005). But later, Tamaddonfard and his group reported that the crocin and diazepam combination has antiepileptic activities in rats at an effective dose of crocin (50 μg) with an ineffective dose of diazepam (2.5 μg). The study revealed that crocin potentiated the anticonvulsants of diazepam through GABAA-benzodiazepine receptor-mediated mechanism.

7.5.2.7 Memory-Enhancing and Anti-Alzheimer's Activity

The saffron extract and its active constituents were evaluated to know the effect to prevent Alzheimer's disease. The saffron extract (30 mg/day) showed better outcome on cognitive function than placebo after 16 weeks (Akhondzadeh et al. 2010a). In another study, it was observed that use of same dose for 6 months produced equivalent effect as that of donepezil (10 mg/day; Akhondzadeh et al. 2010b).

7.5.2.8 Antitumor Activity

Saffron and its chemical compounds have been evaluated for the therapeutic potential against the variety of cancers. The crocin-, picrocrocin-, and safranal-containing saffron stigma extracts reported to inhibit the growth of human tumor cells (Bhandari 2015; Escribano1996). Anti-proliferative activity on HCT-116, SW-480, and HT-29 (colorectal cancer) cell lines revealed that saffron and its major constituents restricted the proliferation of cancerous cells (Aung et al. 2007).

7.5.2.9 Cardiovascular Effect

Saffron and its bioactives exhibited cardioprotective characteristics in the evaluation of preclinical studies. Aqueous extract of *C. sativus* (20, 40, 80, and 160 mg/kg) and safranal (25, 50, 75 mL/kg) were reported to reduce the level of MDA content lipid peroxidation and level of MDA in the heart. CK-MB and LDH activities were reduced in serum of Wistar rats due to the effects of saffron and its bioactives (Mehdizadeh et al. 2013). Moreover, crocetin (50 mg/kg/day) prevents the inflammations and protects MIRI in rats by inhibiting ROS production. It has also shown reduction in myocardium apoptosis (Wang et al. 2014).

7.5.2.10 Antinociceptive and Anti-Inflammatory Activities

The petal and stigma of saffron have antinociceptive as well as anti-inflammatory potentials. These effects were might be due to the presence of bioactive agents of *C. sativus* (Hosseinzadeh and Younesi 2002).

7.5.2.11 Hypolipidemic and Hypoglycemic Activities

Crocin (100 mg), an important constituent of *C. sativus*, was found effective for patients with metabolic syndrome. The treatment for 1.5 months has shown reductions in the content of triglycerides and total cholesterols. This suggests the hypolipidemic potential of saffron. Further, the water extract of stigmas relieves cognition skills in the diabetic encephalopathy rats. It was observed that at a dose of 20, 40, and 80 mg/kg/day, the reduction in glucose levels was started at fourth, second, and first week of the extract administration, respectively (Kermani et al. 2017; Samarghandian et al. 2014).

7.5.2.12 Diuretic Activity

The diuretic activity of crocin and aqueous extract of saffron stigmas (60, 120, and 240 mg/kg) was reported by Shariatifar and workers (2014a, b). The results were calculated based on urine volume, electrolyte concentrations, creatinine, and urea. Thus, saffron extracts showed dose-dependent increment in the excretion of

electrolytes, while crocin significantly increases the content of creatinine and urinary nitrites in urine of the rats (Hassanin 2015).

7.5.2.13 Cytotoxic Activity

In cytotoxic studies, saffron extracts (100, 200, 400, and 800 μg/mL) reduced the VEGF-A and VEGFR-2 gene expression in MCF-7 cell lines in comparison to control. The decline in VEGF-A (17%) and VEGFR-2 (20%) in gene expression at 800 and 400 μg/mL, respectively, was noted (Mousavi and Baharara 2014). Saffron extract and combination of crocin and safranal gave IC_{50} values at 71 μg/mL and 39 μM for the antiproliferative activity against lymphoblastic T-cell leukaemia (Makhlouf et al. 2016). The saffron extract, crocin, and picrocrocin have shown cytotoxic and apoptogenic effects in malignant TC-1 and non-malignant COS-7 cell lines (Mykhailenko et al. 2019). The crocin (0.05–4 mM) and safranal (0.2–3.2 mM) showed significant cytotoxic effects against oral squamous cell carcinoma KB cells as well as NIH/3 T3 cells with the IC_{50} 2.8 and 0.3 mM, respectively (Mykhailenko et al. 2019). The safranal also inhibited the proliferation of neuroblastoma cells with IC_{50} value of 11.1 and 23.3 μg/mL after 24 and 48 h, respectively. Moreover, the saffron corms bioactive combination (carbohydrates and protein) was found cytotoxic against human cervical epithelioid carcinoma cells (IC_{50}, 7 mg/mL; Escribano et al. 1996, 2000). The triterpenoid saponins from corms were also active against HeLa tumoural cells (Mykhailenko et al. 2019).

7.5.2.14 Toxicity

C. sativus is considered safe even at a dose of more than1.5 g/day (Milajerdi et al. 2016). In animals, its lethal dose is 20.7 g/kg and no toxicity up to a dose of 5 g/kg was noticed. Isolated compounds crocin and dimethyl-crocetin were not found toxic in the Ames/Salmonella assay (Lari et al. 2015; Mykhailenko et al. 2019).

7.5.3 Standards and Criteria

7.5.3.1 Collection Period

The flowering of saffron remains only for 3–4 days and should be collected on the appearing of first flower. As the quality of flowers is affected by wind, sunlight, or heat, the best collection period is between October and November and should be done at dawn (Evans 1997; Kafi 2002).

7.5.3.2 Collection Method

Collection of flowers should be done by hand. Flowers have to be opened on the same day of collection. Opening of flowers before collection may lead to the destruction of stigmas and ultimately mixing with petals which will decrease the quality (Evans 1997; Hemmati Kakhki 2001).

7.5.3.3 Drying Methods

Stigmas must be dried for storage purposes. Quality and hence cost of saffron are mainly affected by drying process. Traditionally, stigmas were dried by putting them in baskets containing holes and hanging them on the roof at an appropriate temperature. Drying completes when the colour of stigmas changed to dark red. But this method was long and took around 10 days for drying. In the last few decades, the use of electric ovens is in trend. The recent method employed the use of a sterile silk net placed in the oven at 50–60 °C which gives high quality and fast drying (Dadkhah et al. 2003).

7.5.3.4 International Standards of Plant Material

The chemical characteristics of dried saffron as per ISO 3632-1 are depicted in Table 7.2. One of the main quality parameters is the measurement of colouring power through crocin, picrocrocin, and safranal) using ultraviolet-visible (UV-Vis) spectrophotometry. The colouring power of three quality categories for saffron threads at 440 nm should be 190, 150, and 100 units, respectively. In addition, the moisture content and maximum non-soluble ash content were also specified, and details are depicted in Table 7.2 (ISO/TS 2003).

7.5.3.5 Food and Drug Administration Criteria

Based on the FDA (Hemmati Kakhki 2001), the material must have the following properties:

- Stigmas must be yellow and foreign matter should not be >10%.
- The volatiles and humidity must not be >14% when the saffron dried at 100 °C.
- The total ash not >1% while soluble ash should not >1%.

Table 7.2 Chemical characteristics of dried saffron on the basis of ISO 3632-1

Main characteristics	Saffron powder (%)	Saffron thread (%)
Volatile substances and humidity content	10	12
Crude ashes (mass percentage) in dry matter	8	8
Non-soluble ashes in HCl (mass percentage) in dry matter		
For Grades 1 and 2	1	1
For Grades 3	1.5	1.5
Maximum picrocrocin absorption value at 257 nm		
Grade 1	70	70
Grade 2	55	55
Grade 3	40	40
Maximum safranal absorption value at 330 nm	20–50	20–50
Maximum crocin absorption value at 440 nm		
Grade 1	190	190
Grade 2	150	150
Grade 3	110	110

7.5.3.6 Adulterants

To reduce the cost of saffron, mixing is observed with beet, pomegranate, and red dyed silk fibres (Hagh-Nazari and Keifi 2007). In addition, the stamens of saffron are often adulterated with *Carthamus tinctorius* (safflower), *Calendula officinalis* (marigold), arnica, and tinted grasses to increase the product mass. Turmeric and paprika are combined with saffron powder. The labeling of *Curcuma longa* as "Indian saffron", "American saffron", or "Mexican saffron" also misleads the people. Besides, artificial colourants are another common way of adulteration (Kafi 2002).

7.5.3.7 Purity Check

Chemical Test

- Saffron shouldn't include yellow styles.
- When pressed between filterpaper, it should not leave an oily stain.
- When chewed, it should give a deep orange-yellow colour to the saliva.
- When soaked in water, it should immediately dissolve and give a distinct yellow colour.
- No colour is imparted to benzene when agitated with saffron.
- Saffron extract gives a purple-blue colour when comes in contact with sulphuric acid.

7.5.3.8 Other Methods

Other methods include microscopic studies, colorimetric reactions, chromatographic techniques, TLC, and HPLC. HPLC is considered the most reliable technique (Hagh-Nazari and Keifi 2007). A colorimetric reflection method is based on CIE system where L* is brightness, a* redness-greenness, and b* yellowness-blueness, and correlated with the colouring power on samples (Alonso et al. 2003).Also, the atmospheric chemical ionization-mass spectrometry technique is a sensitive and easy method for quantitative analysis of volatile compounds (Taylor and Linforth 2003). Fourier transform near-infrared spectroscopy technique is also introduced for quality analysis of saffron that does not require any sample treatment (Zalacaín et al. 2003).

7.5.4 Commercialized Formulation

- The topical polyherbal formulation (itch cream) for xerotic and pruritic skin disorders has been prepared with the ingredients (v/w basis): *Curcuma longa* (16.0%), *C. sativus*(0.025%), *Santalum album* (8.0%), vetiver (0.5%), *A. moschatus* (0.1%), *Lawsonia inermis* (3%), *Ocimum sanctum* (3%), and *Glycyrrhiza glabra* (0.5%) extracts, curcuma oil (6.1%), Surasar (0.5%), and Swarna Bhasma (0.00032%) in a non-greasy cream base q.s. (Chatterjee et al. 2005).
- Scar removal skin cream (100 g) ingredients: wheat germ oil (3.5 mL), turmeric (20 g), neem (2 mL), sandal wood (1 mL), orange (2 g), rosemary oil (5 mL), *A. vera* gel (2 mL), saffron (1 g), cream base q.s. (Kalia 2005).

- Tincture dose—5–20 min.
- Saffron tea 1 in 80 (infusion).

7.5.5 Conclusion and Future Prospects

C. sativus is an important medicinal as well as food crop widely cultivated for nutritional and flavour purposes. In this book chapter, we tried to summarize the traditional claims, standardization methods, phytochemistry, pharmacological potential, and commercialized products of all parts of saffron. Besides, various physical parameters like temperature, humidity, wind, and methods that affect quality (flavour and colour) of saffron were also discussed. The main challenge is to meet the raw product demands that make it expensive in international market. Carotenoids, phenolics, and flavonoids are the main classes of secondary metabolites that are found in saffron. The main active constituents crocin, crocetin, and safranal are potential antitumor, anti-inflammatory, antiparasitic, and antibacterial agents. However, the effects have been slightly evaluated in humans. It would be interesting to see these effects in clinical trials.

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Positive Health Benefits of Saponins from Edible Legumes: Phytochemistry and Pharmacology

8

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Abstract

Saponins are the naturally occurring phytochemicals present in most vegetables, edible legumes, and herbs. These constitute a chemically diverse group of compounds that contain steroid or triterpenoid aglycone linked to one or more oligosaccharide moieties. These compounds are characterized by surface-active foaming properties, bitter taste, and astringency. Numerous studies have suggested the positive health benefits of saponins on blood cholesterol levels, bone health, blood glucose level, and cancer risk. A diet rich in saponins has been shown to reduce dental caries, inhibit platelet aggregation, treat hypercalciuria, and act as an antidote against heavy metal poisoning. The present review summarizes the phytochemistry and pharmacology of saponins derived from edible legumes and also highlights their positive health benefits.

Keywords

Saponins · Phytochemistry · Pharmacology · Health benefits · Glycosides

8.1 Introduction

Saponins are naturally occurring amphipathic surface-active glycosides present in a variety of edible legumes having distinctive foaming characteristics. These are the secondary compounds occurring in various edible and inedible parts of the plant, for

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example, leaves, stem, bark, root, etc. They are also produced by some bacteria and lower marine animals (Riguera 1997; Yoshiki et al. 1998). The name "saponin" is derived from the Latin word Sapo (*Saponaria*) meaning stable soap-like foam formation in aqueous solutions. Saponins consist of a triterpene or steroid moiety known as aglycone, which is glycosidically linked to one or more sugar chains known as glycone (Tava and Avato 2006). Due to lyobipolar character, saponins decrease the surface tension of aqueous solutions and also interact with membrane of cells (Melzig et al. 2001).

On the basis of differences in aglycon structure and sugar moiety, saponins can be classified as mono-, bi-, and tridesmosidic (Rehan et al. 2020). The primary source of saponins is plants and algae with rare reports from microbial sources. These are particularly abundant in the Fabaceae plants (Tava and Avato 2006). The content of saponins in a plant depends upon the age and the part of the plant. The germinated seeds have higher saponin content than the dry seeds. Various plant species such as *Ilex paraguariensis*, *Bacopa monnieri*, *Panax ginseng*, *Glycyrrhiza*, and *Chlorophytum borivilianum* are rich source of saponins (Kaur et al. 2015). In addition to these, a wide diversity of saponins are also reported from plants such as *Yucca schidigera*, *Quillaja saponaria*, *A. auriculiformis*, *Sapindus saponaria*, *Sesbania sesban*, and *Medicago sativa* (Belanche et al. 2015). This varied presence of saponins in plant kingdom is attributed to their bitter taste which helps in protecting the plant from being eaten by stray animals (Ikeuba and Okafor 2019). Saponins possess foaming, pharmacological, medicinal, and hemolytic properties and also find a place in cosmetic, beverage, and confectionery industries (Kajal and Singh 2017). Medicinal properties include hemolytic factor (Hassan et al. 2010), anti-inflammatory (Just et al. 1998), antibacterial (Sparg et al. 2004), antifungal (Sindambiwe et al. 1998), antiviral (Simões et al. 1999), insecticidal (De-Geyter et al. 2007), anticancer (Cheng et al. 2011), cytotoxic (Mbaveng et al. 2018) and molluscicidal (Abdel-Gawad et al. 1999) action. In pharmaceutical industry, saponins are widely considered as precursors for the synthesis of steroidal drugs (Waheed et al. 2012).

Pulses are edible seeds of legumes, harvested exclusively for dry grain, and used for human consumption (Mudryj et al. 2014). These include peas, beans, chickpeas, beans, lentils, flageolets, etc. Pulses are among the most cultivated and extensively consumed staple food in the world and have been used for at least 10,000 years (Mudryj et al. 2014). These are recognized as one of the most important crops in the world due to their nutrition as well as health-promoting benefits (Tiwari and Singh 2012). Pulses have high fiber, low lipid, and basic protein content and form the main plant source of macronutrients and minerals (Rochfort and Panozzo 2007). They also serve as a rich source of secondary metabolites, viz., saponins, phytates, tannins, oxalates, lectins, phytosterols, polyphenols, etc., having potential health benefits (Dilis and Trichopoulou 2009). The bioactive substances present in pulses have been recognized to exhibit various effects in humans such as enzyme detoxification, hormone metabolism regulation, antioxidant, immune system stimulation, anti-angiogenic, etc. (Campos-Vega et al. 2010; Singh et al. 2017). Saponins in legumes have attracted considerable attention and have been reported in lupins

(Woldemichael et al. 2003), lentils (Ruiz et al. 1996), and chickpeas (el-Adawy 2002), as well various beans and peas (Shi et al. 2004).

8.2 Structure and Biosynthesis

Saponins are natural bioactive compounds widely present in plant kingdom and occur as active constituents in more than hundred families including organisms of marine and terrestrial origin, but are not common in higher animals (Van Dyck et al. 2010). The chemical diversity of saponins is attributed to a wide range of biological activities as given in Table 8.1.

Saponins are glycosides composed of carbohydrate part (glycone) and non-carbohydrate part (aglycone). The aglycone moieties are often called as sapogenins. The aglycone moiety is attached via an ether bond at C3 to a sugar side chain, but many saponins have an additional sugar moiety at C26 or C28 position. The sugar moiety present in saponins is usually galactose, glucuronic acid, xylose, glucose, or rhamnose (Francis et al. 2002). The hypothetic saponin structure is shown in Fig. 8.1.

Saponins having one, two, or three sugar chains attached to aglycone part are known as monodesmosides, didesmosides, or tridesmosides. These are biosynthesized from mevalonic acid pathway as shown in Fig. 8.2. Two isopentenyl diphosphate units (IPP) condense with dimethylallyl pyrophosphate (DMAPP) to form farnesyl pyrophosphate (FPP) which is a 15-carbon compound. In the presence of squalene synthase (SQS), two FPP units condense to form squalene (30 carbon precursor), which is further epoxidized by enzyme squalene epoxidase (SQE) to 2,3-oxidosqualene. The oxidosqualene cyclases (OCS) cyclize 2,3-oxidosqualene to polycyclic structures (Weng et al. 2011).

Table 8.1 Biological activities of saponins

S. No.	Biological activity	References
1	Antimicrobial activity	Francis et al. (2002)
2	Anti-inflammatory activity	Sparg et al. (2004)
3	Antifungal activity	Murray et al. (2001)
4	Anti-cancer activity	Podolak et al. (2010)
5	Anti-viral activity	Sparg et al. (2004)
6	Immunomodulating activity	Kim et al. (2003)
7	Hypoglycemic activity	Matsuda et al. (2002)
8	Anti-osteoporosis effect	Zhang et al. (2012)
9	Anxiolytic and nootropic activity	Une et al. (2001)
10	Analgesic activity	Khan et al. (2011)
11	Antihistaminic activity	Nurul et al. (2011)
12	Antioxidant activity	Xiangyang et al. (2002)
13	Anti-ulcer activity	Marhuenda et al. (1993)
14	Anti-aging activity	Ramalingam and Kim (2016)

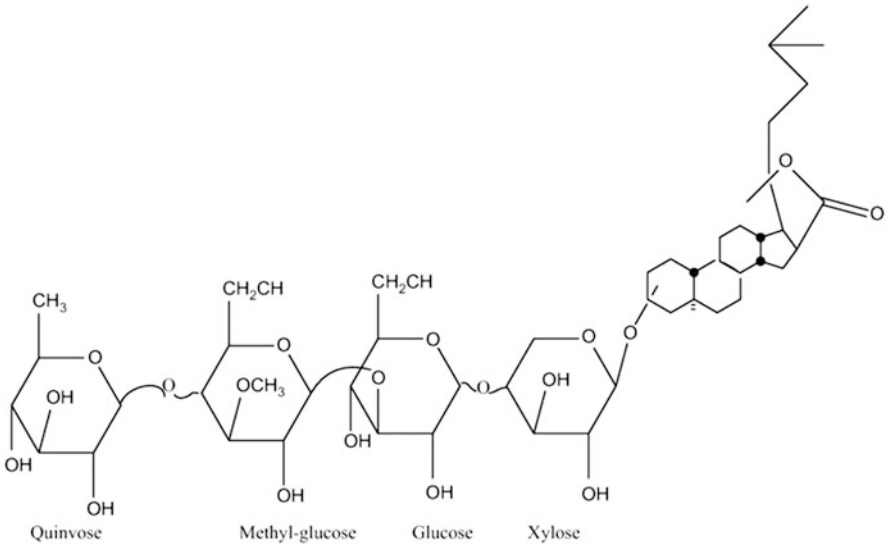

Fig. 8.1 Molecular structure of hypothetic saponins composed of an aglycone and a linear glycosidic chain consisting of monosaccharides, namely, quinovose, methyl-glucose, glucose, and xylose. *Source:* Caulier et al. (2011)

8.3 Classification

Saponins are classified on the basis of chemical character of the aglycone into triterpenoid and steroid saponins (Fig. 8.3). Structurally these vary widely depending on the nature of side chains, aglycone, and position at which aglycone moieties are attached.

8.3.1 Triterpenoid Saponins

Triterpenoids are widely distributed in plant kingdom especially in families like *Amaranthaceae*, *Apiaceae*, *Leguminosae*, *Cucurbitaecae*, *Caryophyllaceae*, *Berberidaceae*, *Aquifoliaceae*, *Myrsinaceae*, *Zygophyllaceae*, and *Chenopodiaceae* (Parente and da Silva 2009; Sparg et al. 2004). These saponins are comprised of a triterpene aglycone linked to one, two, or three saccharide chains of varying size and complexity. Triterpene aglycone is composed of four- or five-ring configuration of 30 carbons with several oxygens attached. In the gut the saccharide or sugar molecules are cleaved by microbes releasing triterpene (Xu et al. 2004). Legumes such as beans, soybeans, horse chestnut, ginseng, sunflower, and peas are rich source of triterpenoids (Osbourn et al. 1994). Structure of some triterpenoids isolated from legumes is shown in Fig. 8.4.

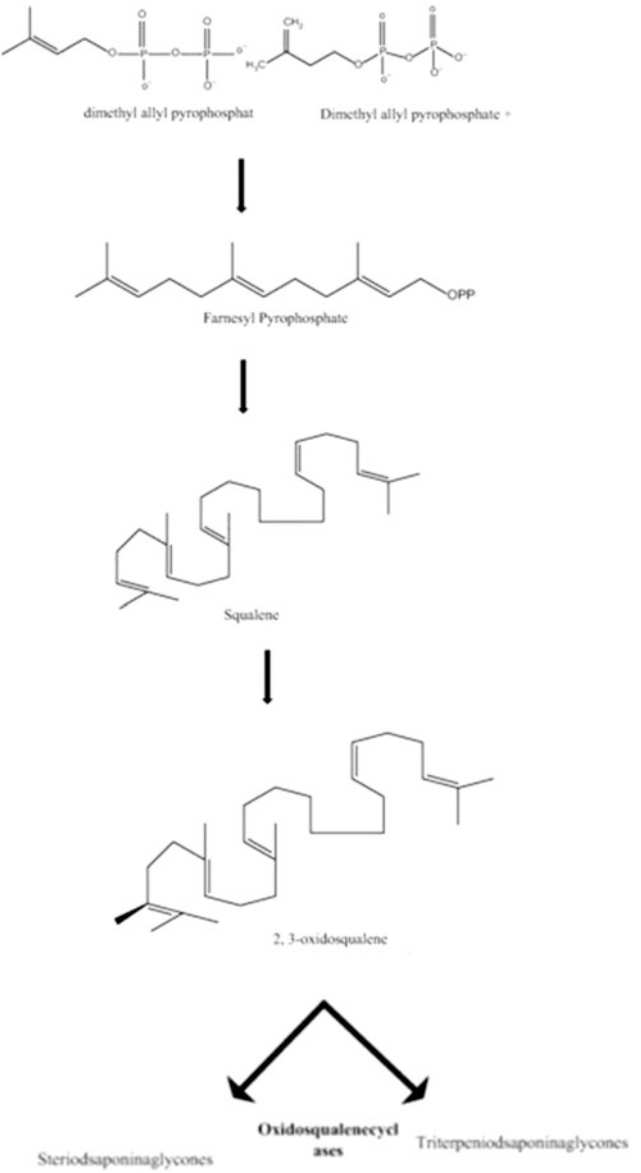

Fig. 8.2 Synthesis of saponins from mevalonic acid pathway (Weng et al. 2011)

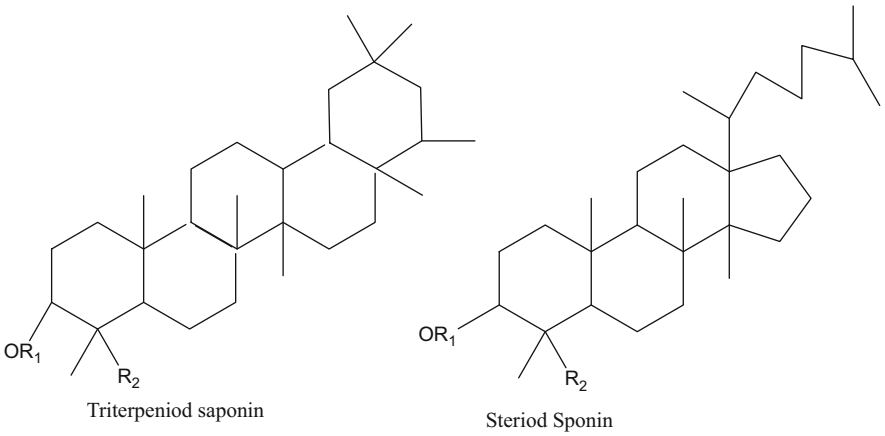

Fig. 8.3 Structure of triterpenoid and steroid saponins (Francis et al. 2002)

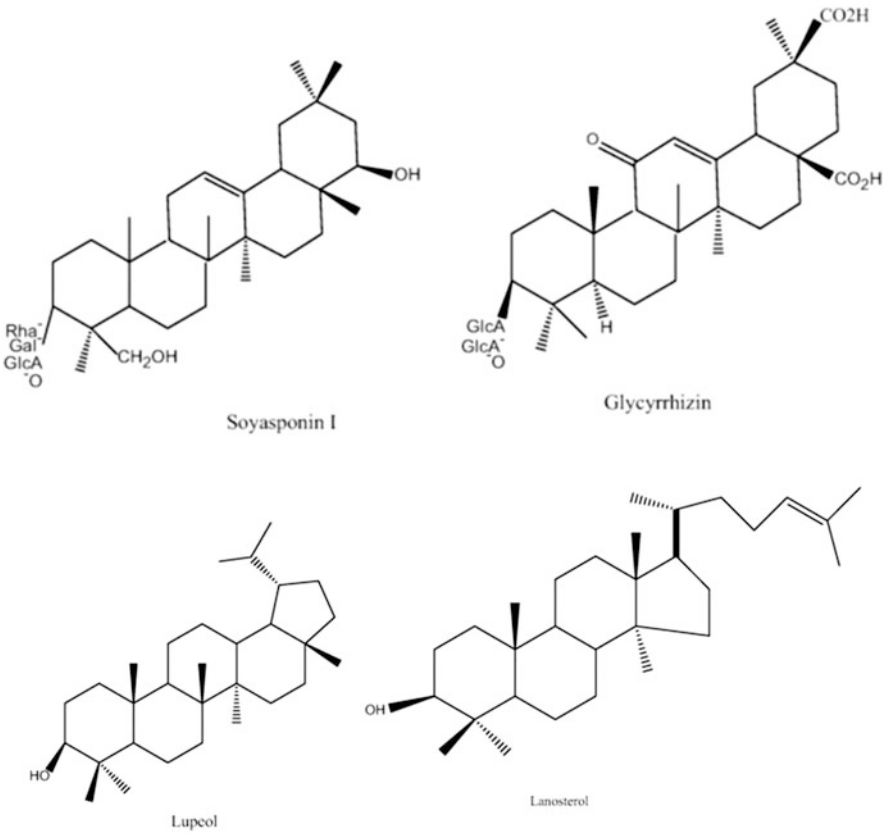

Fig. 8.4 Triterpenoid saponins: avenacin A-1 from oat roots, chromosaponin I from peas, ginsenoside Rg 1 from ginseng roots, avicin D from seed pods, soyasaponin I from soya, and glycyrrhizin from liquorice roots (Dixon and Sumner 2003; Hartmann 2007; Osbourn et al. 2011)

The important classes of triterpenoid saponins are hopanes, lanostanes, oleananes, ursanes, tirucallanes, taraxsteranes, and cucurbitanes as depicted in Fig. 8.4. Oleananes are pentacyclic triterpenoids found in Solanales, Rhamnales, Juglandales, and Zingiberales (Vincken et al. 2007). Ursanes are less abundant pentacyclic triterpenoids identical to oleanane but differ in location of one methyl group. Ursolic acid and oleanolic acid have been exploited for cytotoxic activity against lymphoma cells and human leukemia (Chiang et al. 2003).

8.3.2 Steroidal Saponins

Steroidal saponins are found in the families of Scrophulariaceae, Alliaceae, Bromeliaceae, Palmae, Agavaceae, Liliaceae, Asparagaceae, Dioscoreacea, Amaryllidaceae, Smilacaceae, and Solanaceae (Waller 1996). Steroidal saponins are present in large quantities in plants such as asparagus, ginseng, yucca, yam, allium, and fenugreek (Hoffmann 2003). Steroidal saponins have 27 carbon atoms, comprising of 4 core structures, lactone-bearing cardenolide, tetracyclic cholestane, pentacyclic furostane, and hexacyclic spirostane as shown in Fig. 8.5.

Spirostane steroidal saponins are mainly derived from disognyl glycosides and have shown promising pharmacological activities such as anticancer, antithrombotic, and neuroprotective activities (Parama et al. 2020; Wang et al. 2013). Tigogenin isolated from *Yucca gloriosa* L. showed a good antitumor activity in various cancer cell lines (Gu et al. 2014). Furostane saponins contain hemiketal ring and carbohydrate part attached to the 26-OH and/or 3-OH of sapogenin. Practically furostane is synthesized from readily available 16β-acetyl-22-oxo-cholestanic derivative (Guan et al. 2012; He et al. 2006). The pharmacology of furostane has revealed that it causes the inhibition of α-glucosidase with $IC_{50} = 96\ \mu M$ and is 12 times stronger than acarbose (P. Wang et al. 2016).

8.4 Phytochemistry

The structural diversity of saponins results in their diverse physicochemical properties. Saponins are surface-active agents with foaming, detergent, emulsifying, and wetting properties. These properties are attributed to the presence of water-soluble sugars and lipid-soluble aglycone (Ibanoglu 2000; Sarnthein-Graf and La Mesa 2004; Z. Wang et al. 2005). Saponins are well soluble in aqueous solutions; the water-soluble sugar residues are extensively hydrated when dissolved in water (Sarnthein-Graf and La Mesa 2004). Saponins align themselves vertically on the water surface with their lipid-soluble aglycones oriented away from aqueous phase. This reduces the surface tension of water, resulting in the formation of foam. The surface-active property of saponins allows them to form micelles in aqueous solutions above a critical concentration called critical micelle concentration (Cheeke 1989). The micelle formation is affected by various parameters, e.g., it increases with pH and temperature but decreases with high salt concentration. The location and

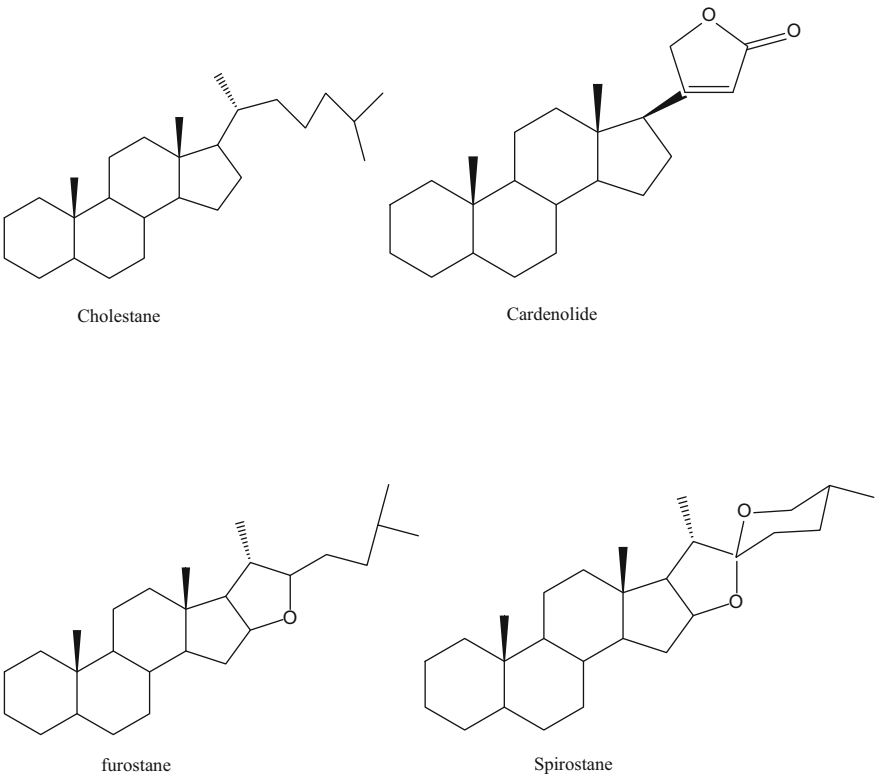

Fig. 8.5 Representative core structures of steroid saponins (Lorent et al. 2014)

presence of carboxylic acid group in the saponin molecules may impact the surface activity. In aqueous phase the –COOH group dissociates and forms free carboxyl anion, accountable for increasing solubility of saponins in aqueous phase (Mitra and Dungan 2000).

Saponins are natural phytoconstituents, able to form foam, and a useful property in cosmetic, food, and pharmaceutical processes. The shear viscoelasticity and high dilational property of saponins at air/water interface is responsible for high stability and foamability of saponins from various plant extracts of *Quillaja saponaria*, *A. hippocastanum*, and *Camellia oleifera* (Golemanov et al. 2013; Pagureva et al. 2016). The less amount of sugar residues in saponins results in high instability of foam due to formation of only few intermolecular H bonds between sugar residues leading to a weak interfacial network (Golemanov et al. 2013).

Saponins reduce interfacial tension at the O/W interface and form small oil droplets. Kinetically emulsions are stable when dispersed oil droplets are nanosized due to slowdown of phase separation. Measurement of zeta potential in quillaja saponins has shown stabilized emulsion formation due to electrostatic repulsion (Maier et al. 2015; Yang et al. 2013; Zhang et al. 2016). Quillaja saponin emulsions

are stable in a broad range of environmental factors like pH, temperature, and ionic strength. As a result, quillaja saponins have currently found commercial application in food products as emulsifying agents with proteins of egg and milk such as egg lysozyme or β-casein and β-lactoglobulin (Kezwon and Wojciechowski 2014).

8.5 Pharmacology

Saponins are glycosides having surface-active property. They occur naturally in wide variety of plants, some bacteria, and also some lower marine animals. The content and composition of saponins in a plant vary markedly depending on the genetic background, tissue type, and age of the plant. A number of pharmacological actions (Fuchs et al. 2009; Kensil 1996; Setzer and Setzer 2003; Sun et al. 2009) have been attributed to them, some of which are beneficial while some are detrimental to human well-being. Their important actions include insecticidal, antifungal, anthelmintic, immunostimulant, cytotoxic, anti-inflammatory, hypocholesterolemic, hypoglycemic, and abortifacient activities (Francis et al. 2002). They also have an effect on permeability of cell membranes and cause hemolysis of RBCs (Takechi et al. 2003).

8.5.1 Anti-Inflammatory Activity

Inflammation is the biological response to harmful stimuli, such as autoimmune diseases, pathogenic infections, damaged cells, and irritants. Various studies have demonstrated that triterpenoid saponins from *A. victoriae* could react with cysteine residues in the nuclear transcription factor-kB (NF-kB) and alter it to prevent from performing its normal function of stimulating genes involved in the inflammatory pathways. Phospholipase A2 is another important effector substance, whose activity is lowered by saponins, which causes a decrease in hydrolysis of membrane phospholipids and thereby decreasing membrane fluidity (Cabral de Oliveira et al. 2001).

8.5.2 Antimicrobial Activity

Antimicrobial activity of saponins against medically important Gram-positive and Gram-negative bacteria has been investigated (Avato et al. 2006; Soetan et al. 2006). Activity is especially high against Gram-positive organisms (*B. subtilis*, *B. cereus*, *Staphylococcus aureus*, and *Enterococcus faecalis*). The activity against Gram-negative bacteria is relatively low, as cell membranes of these microorganisms are not penetrable by some of these saponins.

8.5.3 Hypoglycemic Activity

Saponins isolated from plants like fenugreek, *Phellodendron* cortex, *Aralia* cortex, and *Calendula officinalis* (Kim et al. 1998) have been shown to possess hypoglycemic effects (Petit et al. 1993). This action is thought to be due to suppression of glucose transfer from the stomach to the small intestine and inhibition of glucose transport across the brush border of the small intestine.

8.5.4 Effect on Cholesterol Metabolism

Consumption of several dietary saponins such as chickpea, lucerne, and soya bean (Oakenfull 1986) has been shown to have hypocholesterolemia action in some animals and humans (Hirsch et al. 1962; Potter et al. 1993). Saponins interact with bile acids resulting in the formation of large mixed micelles, which account for increased excretion of cholesterol. Micellar bile acid molecules are not available for reabsorption and hence diverted from the enterohepatic cycle (Sidhu and Oakenfull 1986). This augmented metabolism of cholesterol causes its serum level to go down.

8.5.5 Effect on Cell Permeability

Enormous biological effects of saponins have been attributed to their action on cell membranes; in fact they have a specific ability to form pores in membranes (Authi et al. 1988; Izzi et al. 1992). Saponins are well known for causing lysis of erythrocyte membranes, and this very property has been used for their detection. The affinity of the aglycone moiety for membrane sterols, particularly cholesterol, is believed to be responsible for the hemolytic action of saponins (Bangham and Horne 1962). Saponin molecules are arranged in a ring, and their lipophilic moieties combine with cholesterol in a micelle-like form around the outer perimeter in the plane of membrane (Bangham and Horne 1962). Brain and colleagues (Brain et al. 1990) reported that inclusion of aglycone part into the lipid bilayer is independent of the presence of cholesterol. It has been shown that if saponins are glycosylated both at C3 and C28 (bidesmosidic) positions (Hu et al. 1996), they would result in alteration of permeability on liposomal membrane irrespective of cholesterol. The abundance of cholesterol exhibits inhibitory effect on many membrane ATPases. It can directly interact with the boundary lipids of ATPase and modify the intermolecular hydrogen bonds of the protein.

8.5.6 Virucidal Activity

Some saponins and sapogenins are able to deactivate the viruses; Sindambiwe and colleagues (Sindambiwe et al. 1998) in a study showed that a purified saponin mixture from *Maesa lanceolata* inhibits HIV-1 virus replication. Mengoni and

colleagues (Mengoni et al. 2002) observed that oleanolic acid, a triterpenoid sapogenin, also inhibited HIV-1 virus replication. This inhibition of viral replication was thought probably due to inhibition of HIV-1 protease activity.

8.5.7 Effects on Immune System

Adjuvants based on saponins have the exclusive ability to stimulate the cell-mediated immune system. These also augment antibody production. They have the advantage as only a low dose is needed for the particular activity (Oda et al. 2000). Also, saponins are said to induce production of interleukins and interferons like cytokines that mediate the immunostimulant effects (Jie et al. 1984).

8.5.8 Cytostatic Effects on Malignant Cells

Saponins isolated from various animals and plants specifically inhibit the growth of cancer cells (Kuznetsova et al. 1982). Fries et al. (2006) reported that saponins isolated from the sea cucumber exhibit anticancer activity. Results from more than 400 studies have reported the ability of saponins to treat cancer or induce programmed cell death. Among these studies, almost 90% were carried out by in vitro techniques where the rest have been carried out by in vivo methods using mice as an animal model. Only 24% of studies have been conducted on different human cancer cell lines like MCF-7, MDA-MB43, HeLa, Caco-2, and Hep-G2, which represent breast, colon, cervical, and hepatic, respectively. The basic saponin structure for cytotoxic activity seems to be Kalopanaxsaponin-A, produced by bacterial action on hederagenin glycosides in the intestine. Avicins from *A. victoriae*, a triterpenoid saponin, selectively inhibits the growth of human breast cancer cell line (MDA-MB-453) by cell cycle arrest and programmed cell death (apoptosis) in leukemia and breast cancer cell lines (Mujoo et al. 2001) and reduces both tumor incidence and multiplicity in a murine skin carcinogenesis model (Haridas et al. 2001). Secondary bile acids (formed by intestinal bacteria by metabolizing bile acids) are known to be causative agents of colon cancer. Saponins bind to these bile acids and reduce their availability, thus reducing and preventing the formation of carcinogenic substances in the colon (Cheeke 1996) and exhibiting anticancer effects. Metabolites of saponins like ginsenoside M1 produced by the action of microbes on ingested ginseng saponins in the intestine also have shown anticancer activity (Wakabayashi et al. 1998). Higher singular off-target effects and misleading correlation between in vitro and in vivo data complicate their potential use as cytotoxic agents in the clinical setting.

8.5.9 Effect on Protozoa

Steroid and triterpenoid saponins exhibit activity against several protozoas such as malaria caused by *Plasmodium falciparum* (Banerjee et al. 2018), *Leishmania species* (Delmas et al. 2000), and *Giardia trophozoites* (McAllister et al. 2001). The toxicity of saponins to protozoans seems to be nonspecific and is due to their detergent effect on the cell membranes.

8.5.10 Effect on Nervous System

The extract of ginseng has been shown to exhibit neurotrophic and neuroprotective effects. It significantly improved learning ability and cognitive functions in brain-damaged rats in a dose-dependent manner and enhanced the strategic performance of normal rats. These effects are attributed to membrane-stabilizing effect and inhibition of Na^+ and Ca^{2+} channels of ginseng (Zhao and McDaniel 1998). Saponins obtained from *Panax notoginseng* have shown anti-cerebral ischemic effects, which are probably due to changes in the rank and structure of functional membrane proteins which are induced by fluidity of membranes that lead to changes in protein activities (Ma and Xiao 1998).

8.5.11 Other Effects

- Saponins exhibit abortifacient, anti-zygotic, and anti-implantation properties. They are found to be extremely strong stimulators of luteinizing hormone release from cultured hypophysial cells (Benie et al. 1990).
- Dental caries and platelet aggregation can be inhibited by taking a saponin-rich diet.
- Saponins can be used as antidote against acute lead poisoning.
- Hypercalciuria in humans can be treated with saponins. In epidemiological studies, saponins have shown to have an inverse relationship with the incidence of renal stones (Patel et al. 2012).
- Saponins are known to damage the respiratory epithelia of cold blooded animals and, therefore, are toxic to creatures like snake/fish. They are also the active components of many traditionally used fish poisons, like mahua oil cake. Fish also develop stress reactions to saponins in water.
- Saponins extracted from many other sources have to have similar molluscicidal properties, for example, purified *Sesbania sesban* saponins have shown activity against *Biomphalaria glabrata*. Saponins have a characteristic detergent effect on the soft body membranes of mollusks which explains their molluscicidal activity (Dorsaz et al. 1988).

8.6 Bioavailability

Generally, saponins have low bioavailability. Their absorption in the human diet is highly erratic and depends on many factors like amount of saponins consumed in a meal, interaction with bile acids, their method of processing, and metabolic variation of individuals to dietary saponins. They impart a bitter taste at high concentrations (Liener 1994), which limits their consumption by humans and animals. Their bitter taste has also been shown to reduce feed intake by pigs and rats (Cheekei et al. 1978). Acetyl-soyasaponins taste more bitter than non-acetylated constituents (Shimoyamada et al. 1990). Furthermore, when saponins interact with zinc and iron, insoluble phytate mineral complexes are formed that further attenuate the bioavailability of both saponins and the minerals. In some of the animal studies, rats fed with demineralized soy flour and pigs with alfalfa meal had decreased zinc absorption (Pond and Yen 1985; Topping et al. 1978). Similarly, saponins from soya beans and alfalfa decreased absorption of iron in rats (Price et al. 1987).

8.7 Health Benefits

Pulses (lentils, peas, and beans) are the edible legumes that have been consumed and cultivated globally for more than 100 centuries (Leterme and Muñoz 2002). These are commonly used as pilaf, soup, salad, or mixed with meat in the Mediterranean, India, and Middle East. Diverse variety of pulses are grown worldwide and are valued for their health and nutritional qualities. They act as important ingredients in a number of dietary foods, associated with reduced risks of Alzheimer's, parkinsonism, type 2 diabetes, cancer, and cardiovascular diseases (Alcalay et al. 2012; Scarmeas 2009; Willett et al. 1995). Dietary Approaches to Stop Hypertension (DASH) diet has proven to benefit patients suffering from hypertension (Winham et al. 2007), while gluten-free diet (which includes pulses as one of the main components) has been shown to provide relief to celiac disease patients (Kupper 2005). As many as 11 primary pulses, dry beans (tepary beans, moth beans, rice beans, scarlet runner, black gram, mung, navy, azuki, pinto, and kidney beans), dry broad beans (field beans, broad beans, and horse beans), Bambara groundnut, black-eyed peas, chick peas, dry peas, lentils, pigeon peas, vetch, lupins, and other minor (yam, wingled, jack, and velvet beans), have been recognized by the Food and Agricultural Organization (FAO 1994).

Pulses act as a rich source of protein and fiber, vitamins, and minerals (iron, zinc, folate, and magnesium). Pulses have also proven to be a good source of phytoconstituents such as flavonoids, phenolic acids, tannins, alkaloids, phytosterols, lectins, and saponins. These bioactive constituents are thought to have actions like antioxidants, enzyme detoxification agents, lipid, hormone metabolism regulators, immune stimulants, and antiangiogenic agents (Campos-Vega et al. 2010; Singh et al. 2017). Saponins have been found in many edible legumes such as lupins (Woldemichael et al. 2003; Woldemichael and Wink 2002), lentils (Morcos

Table 8.2 Health benefits/effects of some edible legumes

Pulse	Health benefit	References
Beans	Antiobesity	Pusztai and Bardocz (1996)
	Hypocholesterolemic effect	Pusztai et al. (1998)
	Hypolipidemic effects	Shi et al. (2004)
	Anticancer activity	Chan et al. (2014)
	Angiotensin-converting enzyme (ACE) inhibition	Prakash and Sharma (2014), Ranilla et al. (2008)
	Immune modulation	Reddy et al. (2007)
	Reduce the obesity risk	Pedrosa et al. (2012)
Lentils	Hypolipidemic effects	Faris et al. (2013)
	Anticancer activity	de Mejía et al. (2013)
	Reduce the diabetes risk	Randhir and Shetty (2007)
Lupin	Antidiabetic activity	García López et al. (2004)
	Immune modulator	Sirtori et al. (2004)
Faba beans	Anticancer activity	Turco et al. (2016)
	Modify LDL oxidation	Bhathena and Velasquez (2002)
	Anticarcinogenic potential	Fei Fang et al. (2011)
Chickpea	Anticancer activity	Corbiere et al. (2004), Murillo et al. (2004)
	Estrogenic and antiestrogenic effects	García-Lafuente et al. (2014), Mukai and Sato (2009)
	Antidiabetic activity	Singh et al. (1982)

et al. 2013; Ruiz et al. 1996), and chickpeas (Kerem et al. 2005; Shi et al. 2004), as well as soy, various beans, and peas (Shi et al. 2004) (Table 8.2).

8.8 Conclusion

Pulses are rich source of various micro- and macronutrients having potential metabolic and physiological effects, saponins being one of them. Saponins are a wide variety of phytochemicals present in flowers, roots, barks, fruits, seeds, and leaves of variety of plants and have traditionally been used in folk medicine for the treatment of different ailments. The presence of saponins in pulses has been extensively researched and has shown an enormous diversity in structure and function. There is limited data available on the composition of saponins in various edible pulses and the changes in structure and nature during common processing and cooking methods. Previously, saponins were considered as anti-nutrition factors; however, recent research suggests their vital beneficial effects on health. However, more studies are needed to explore the overall therapeutic potential of various saponins isolated from edible pulses.

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Taraxacum officinale: The Esculent Dandelion as Herbal Medicine

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Abstract

Taraxacum officinale Weber is a perennial herb, which belongs to Family Asteraceae and grows wild in hotter zones of the Northern Hemisphere. The plant is commonly called Dandelion. It is native to Eurasia but also reported in Himalayan region (India), including Alpine meadows. Although, the nature of the plant is weedy, the plant has a great potential to treat a number of ailments. The herb has been utilized as a medicinal herb since ancient times. Dandelion is supposed to be loaded with significant number of bioactive constituents including triterpenes, sesquiterpene lactones, fatty acids, carotenoids, volatile oils, tannins, carbohydrates, phenolic acids, flavonoids, phytosterols, sugars, proteins, calcium, and minerals. Due to the presence of these potent phytoconstituents, it has been traditionally used as a folklore medicine for a vast majority of locals in different parts of the world. Reported literature of the plant available from primary and secondary search engines unveil a number of pharmacological activities of the plant, including hepatoprotective potential, diuretic activity, anti-inflammatory activity, antidepressant activity, hypolipidemic activity, anticancer activity, etc. The aim of this chapter is to provide a detailed review of various therapeutic activities of the plant and phytochemical moieties responsible for the medicinal status of *T. officinale.*

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Taraxacum officinale · Dandelion · Folklore medicine · Phytochemical moieties

9.1 Introduction

Taraxacum officinale Weber, having a place with family Asteraceae (Compositae), is a perpetual herbaceous enduring plant, regularly called "Dandelion." The plant is considered as a weedy animal type (Chen 1955). It has numerous English regular names including Blowball, Lion's-tooth, Cankerwort, Swine's nose, and so forth (Cho and Lee 2010). Its Arabic names include Hindiba and Khasberri (Clare et al. 2009). The species name may be from the Arabic word "Tharakhchakon" (Chen 1955) or from the Greek word "Tarraxos." The plant is local to Eurasia. Its appropriation reaches out to Asia, Europe, North America to calm zone of Northern Hemisphere (Grieve 1931). In India, it is accounted for all through the Himalayas on Alpine knolls and slants. It is broadly and barely dispersed at an altitudinal ranges between 1000 and 4000 m (Hajra et al. 1995). In the Indian Himalayan districts, it is regularly known Dudal, Radam, Bathur, and Haend (Hajra et al. 1995). Dandelion herb has significantly toothed smooth leaves, 5–30 cm long and 1–10 cm wide. It is 3–35 cm in stature, surrounding a rosette of leaves at ground level (Wichtl 1994). It has single, splendid yellow blooms on straight leafless void stems, which ascend out of the point of convergence of the rosette. Each sprout includes a get-together of florets. Blossoms are conveyed from pre-Spring until late gather time. Right when the florets created, they produce fleece seeds, which are viably dissipated by the breeze. Dandelion plants have tap roots, diminishing from 2 to 3 cm wide, and no under 15 cm long. Roots are stout and delicate, and are a dull darker shading apparently and white inside (Ali 1989).

The important intelligent portrayal of *T. officinale* was given by Linnaeus in 1753 as *Leontodon taraxacum* (Jaeger and Charles 1955). Wiggers portrayed the assortment *Taraxacum*, and Georg Heinrich Weber made the present plan in 1780 (Britton and Brown 1970).

T. officinale leaves are rich in fiber, potassium, iron, calcium, magnesium, phosphorus, nutrient A, B, C, thiamine and riboflavin, and protein as mulled over (Jackson 1982; Schmidt 1979). Sesquiterpene lactones concede a brutal taste to the plant, which is especially noteworthy in the leaf yet furthermore in the root particularly when spring accumulated (Kuusi et al. 1985). *T. officinale* is suggested as sustenance source because of the high substance of minerals, fiber, supplements, and fundamental unsaturated fats (Hu and Kitts 2005).

The phytochemical examination showed that TO has a wealth of terpenoid and sterol (essentially taraxacin and taraxacerin), likewise passed on in the roots, leaves, and blossoms. Other terpene/sterol blends consolidate beta-amyrin, taraxasterol, and taraxerol, similarly as free sterols (sitosterin, stigmasterin, and phytosterin) fundamentally related to bile (Koo et al. 2004; Schütz et al. 2006).

9.2 Morphology

The genus *Taraxacum*, family Asteraceae, subfamily Cichorioideae, clan Lactuceae, typically known as dandelion, fuses generally 30–57 collections with various microspecies, divided into nine segments (Vašut and Majeský 2015).

Taraxacum is methodically puzzling in subarctic and northern quiet areas, there are around 2800 known species (Kirschner et al. 2014). *T. officinale* is a basically stemless, lactiferous, enduring herb. The stems are acaulescent, just 1–2.5 cm long, with staggeringly short internodes at or underneath the soil surface (Gier and Burress 1942; Holm et al. 1997). The leaves structure a basal, extended rosette in which each sixth leaf covers (Holm et al. 1997). The basal rosette offers rise to one to different glabrous, unfilled, tube-molded scapes (peduncles), 5–50 cm tall, reducing in width along their length from base to tip. Each scape bears a terminal capitulum (inflorescence) of 2–5 cm expansiveness (Gier and Burress 1942; Gleason 1963; Holm et al. 1997). Each capitulum is subtended by an oval-barrel-molded involucre with lanceolate, brutal, green to tannish, herbaceous bracts, in two sections of phyllaries, with the outer phyllaries shorter and more broad than the internal phyllaries (Holm et al. 1997). The unquestionable midrib of the leaves stretches out in shading from light yellow-green to dull darker red (L. L. Collins, unpublished data, University of Western Ontario, London, ON).

Phenotypic variability in *T. officinale* fabricates its ability to colonize a wide extent of common environment. In cool or dry atmosphere, or in solidly mown greenhouses, the leaves spread largely against the ground to form a prostrate rosette (Longyear 1918; Lovell and Rowan 1991). In more sultry atmosphere or in regions where it is swarmed by taller vegetation, the leaves stay in essentially erect tufts (Longyear 1918). The responsibility for leaves, which resemble those of thistles, and the brutal white latex, are acceptable to changes in accordance with anticipation of brushing animals (Richardson 1985). *T. officinale* demonstrates a wide extent of leaf shapes, from a smooth balanced (youthful) structure to a significantly etched runcinate (grown-up) structure (Sanchez 1971). The length–breadth extent decreases as the leaf number grows (Sanchez 1971) and the extent and significance of section focuses in the runcinate structure are influenced by light, mediated by the phytochrome framework (Wassink 1965; Sánchez 1967). Light power and quality can manage the shape of the leaves with balanced sharp edges, and high power runcinate front lines (Sánchez 1967; Slabnik 1981).

9.3 Ancient Background

History of using herbs to treat diseases and prosperity has been ordinary in human social orders. Vast amounts of drugs are being segregated and isolated from herbs. The remedial plants and herbs are the wellsprings of discretionary metabolites and essential oils of accommodating criticalness. The basic ideal conditions against the helpful usage of remedial plants in various sicknesses and messes are their prosperity other than being traditionalist, reasonable, and adequately available (Damylo and

Frank 1984). Asia and Europe have a crucial unquestionable establishment as for the standard occupations of *Taraxacum*, basically *T. officinale*, *Taraxacum mongolicum*, and *Taraxacum coreanum*. This ordinary data has been the chief clarification behind pondering the potential uses and reap necessities of *Taraxacum*; considerations in America remain uncommon (Martinez et al. 2015).

In Russia, India, and China, dandelion has been used in as a regular society sedate in perspective on its hepatic and hyperglycemic impacts (Kemper 1999). The concerned plant is eaten in the Kashmir valley from times degenerate as a vegetable, by the lactating mothers, as a wellspring of minerals especially calcium. The general public solutions of China, India, and Russia have seen dandelion's effect as a liver tonic. Regular Chinese medication unites dandelion with various herbs to treat hepatitis (Modaresi and Resalatpour 2012). Plants of the genus *Taraxacum* have a long history of usage in standard medication (Martinez et al. 2015; Schuetz et al. 2006). Customary dandelion (*T. officinale*) (Fig. 9.1) is an archaic and popular society cure, considered as an "answer of life" (Hojimatov 1989).

Theophrastus, an ancient Greek scientist, recommended dandelion against spots and liver spots on the skin. In Chinese customary medication, the dried establishments of *T. officinale* have been used as a drug to fix edema (Saeki et al. 2013). As demonstrated by Abu Ali Sino (Avicenna), the smooth juice of dandelion reduces the reality of glaucoma and the squeezed juice is uncommonly useful for liver affirmation and against hydrops, similarly as a solution for scorpion bite.

Various botanists believe that *T. officinale* in Greece, or possibly the northern Himalayas, and spread across over gentle zones to Europe and Asia Minor (Richards 1973; Schmidt 1979; Gail 1994). It is thought to have colonized the Americas post-Pleistocene through Beringia (Richards 1973). Later introductions of *T. officinale* to North America are obfuscated in conflicting cases (Gail 1994). The earliest record is that it was found on the east coast by the Vikings in around 1000 AD; others state it was carried on the *Mayflower*; while others believe the introduction was by later pioneers, who brought it as a nursery plant or a pot herb for helpful purposes (Schmidt 1979; Jackson 1982).

9.3.1 Ethnomedicinal Importance

Dandelion (*T. officinale*) is a wild plant that has been used for an extensive time span as a standard drug in the and treatment of a couple of afflictions. This use is a direct result of the sesquiterpenes, saponins, phenolic blends, flavonoids, and sugars, among others, found in the parts of the plant. The leaves can be eaten cooked or used rough in the of blended greens, soups, and tea, which are recommended as a trademark wellspring of supplements in the late winter (Hudec et al. 2007). *T. officinale*, has been used in legends medicine in the treatment of hepatic issue, irritation, and a couple of women's illnesses, for instance, chest and uterus sicknesses.

The principal referenced use of dandelion as a medicine is in advancement of the Arabian specialists of tenth and eleventh, who talk about it as a sort of wild endive,

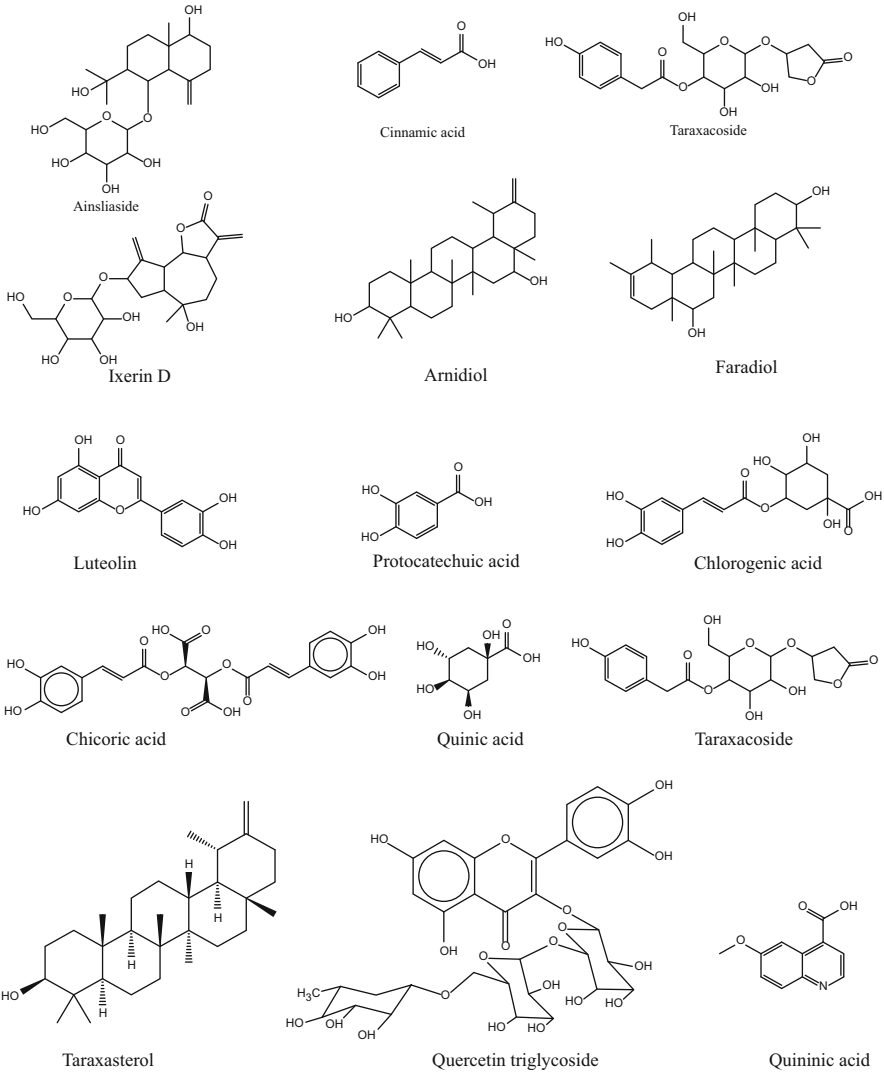

Fig. 9.1 Some bioactive compounds from *Taraxacum officinale*

under the name of Taraxcacon. Dandelion roots and leaves were used to treat liver issues (Grieve 1931). Nearby Americans used gurgled dandelion to treat kidney sickness, swelling, skin issues, indigestion, and irritated stomach (Bensky et al. 1984). In customary Chinese solution, it is moreover acclaimed as a nontoxic herb with exceptional characteristics for its choleretic, diuretic, antagonistic, to rheumatic and quieting properties (Williams et al. 1996). In French writing, dandelion is known for its diuretic activity. In India, dandelion is used in the entire Himalayan belt. In Kashmir, in the Himalaya, paste of gurgled leaves with little measure of salt and

turmeric (haldi) is utilized to treat bone splits (Malik et al. 2011). It is in like manner used as a vegetable in Kashmir (locals experience). In Himachal Pradesh, the roots are used in kidney and liver complaints. The whole plant is pounded into paste and given orally in snakebites and paste is in remotely on wound.

Dandelion has been comprehensively used in regular individuals prescription and in current phytotherapy as a diuretic (the saluretic sway being displayed probably) and a cholagogue. In Chinese, Arabian and Native American traditional prescription it is used to treat a grouping of diseases including harmful development (Clare et al. 2009). In standard drug the plant *T. officinale* has been used for poor assimilation, water upkeep, and against liver illnesses including hepatitis and cirrhosis (as a result of its hepatoprotective effect). Dandelion has been associated in home-developed remedy as a smooth diuretic, for appetite, and for improving osmosis. Its smooth latex has been used as a mosquito repellent (Sohail et al. 2014). *T. officinale* serves fundamentally as a diuretic and as a compound for blood and liver. Dynamic substances of dandelion decline serum cholesterol and triglycerides since they fortify bile discharge. Dandelion improves the limit of liver, pancreas, and stomach. It is moreover used to treat iron inadequacy and affliction; have moderating, against coagulator, unfriendly to oxidative, threatening to malignant growth causing, torment calming, antihyperglycemic, and prebiotic impacts (Abdul et al. 2012; Petkova et al. 2015). *T. officinale* has for a long while been used in normal medication for its choloretic, insect rheumatic, and diuretic properties. In the traditional individuals drug, blends and decoctions from dandelion roots and leaves were moreover used to treat dyspepsia, bronchitis, heartburn, and particular skin defilements. The herb is furthermore used to update the insusceptible response (Onal et al. 2005; Schutz et al. 2006).

9.4 Pharmacological Activities Reported for *T. officinale*

9.4.1 Antioxidant Activity

The production of reactive oxygen species (ROS), which is the outcome of aerobic metabolism and reactive intermediates, occurs in several physiological and pathophysiological states (Jeon et al. 2008). In normal conditions, ROS production is maintained by endogenous antioxidant systems present within the body that sets up a balance between ROS and antioxidants. The excess generation of ROS or inappropriate antioxidant content results in oxidative stress (Kaur et al. 2006). ROS stimulates lipid peroxidation, destroy biomolecules such as DNA and proteins, and has an effect on cellular viability (Jeon et al. 2008).

Oxidative stress is considered to be an essential factor in various neurodegenerative diseases (Beal 1996). The brain is more vulnerable to free radical damage due to the high usage of oxygen by the brain and the presence of quite low concentrations of antioxidant enzymes and free radical scavengers (Muralidhara 2008).

With the aim to gain protection against ROS and to avoid the progression of neurodegenerative diseases, exclusive studies are being done to search new therapies

using antioxidant substances with scavenging ability (Wang et al. 2008). Such antioxidant activities observed in plant extracts had been attributed to polyphenols (Peschel et al. 2006). Polyphenols act as antioxidant via numerous mechanisms such as free radical scavenging, metallic ion chelation, hydrogen donation, and as a substrate for radicals, inclusive of superoxide anion and hydroxyl (Barreira et al. 2008). Flavonoids and phenolic compounds like luteolin, caffeic acid, and chlorogenic acid are determined in extracts of *T. officinale* (Hu and Kitts 2003; Koh et al. 2010). These compounds shield cells from oxidative stress by means of inhibiting the formation of free radicals or by detoxifying free radicals, thus resulting in the prevention of a number of pathophysiological processes (Mates and Sanchez-Jimenez 2000).

Oxidants cause a wide array of DNA damage that includes strand breakage, sister chromatid exchange, and DNA–DNA and DNA–protein cross links in addition to base modifications (Davies et al. 1995). The net result of these modifications can lead to carcinogenesis and mutagenesis (Wei et al. 1998). In both hydroxyl radical and peroxyl radical-induced DNA supercoiled breakage, dandelion fractions exhibited distinct stages of protection toward free radical-induced DNA damage. Flavone glycoside of dandelion flower, namely, luteolin 7-glucoside, provided a protective effect against hydroxyl radical-precipitated DNA scission. Luteolin 7-glucoside also successfully retarded the peroxyl radical-triggered liposome peroxidation, demonstrating that luteolin 7-glucoside specially is an essential antioxidant agent of dandelion flower.

The protective activity of *T. officinale* fruit extract has been investigated against sodium nitroprusside (SNP)-induced decreased cell viability and increased lipid peroxidation in the cortex, hippocampus, and striatum of rats in vitro. To explain the mechanism of the extract's antioxidant activity, its putative scavenger activities against NO•, DPPH•, OH•, and H_2O_2 were determined. The extract (1, 5, 10, and 20 μg/mL) protected against SNP-induced decreases in cellular viability and increases in lipid peroxidation in the cortex, hippocampus, and striatum of rats.

T. officinale fruit extract is a potent antioxidant at low concentrations, as evident by the decrease in lipid peroxidation and protection against SNP-induced cellular dysfunction. One possible mechanism by which *T. officinale* fruit extract protects against oxidative stress is through ROS- and RNS-scavenger activity, which is attributed to phenolic compounds. The phenolic compounds in *T. officinale* fruit extract act as neuroprotective antioxidants or reducing agents (Dirleise et al. 2012a, b, c).

9.4.2 Diuretic Activity

Dandelion (*T. officinale*) was assessed for diuretic activity, that is, it increases the production of urine. The high K+ substance of dandelion is viewed as the specialist in charge of any diuretic movement. As per Duke's USDA database, dandelion has up to nine exacerbates that are diuretic. Given that the saluretic impacts of the dandelion leaf appeared to be because of numerous portions of the extract, the

Table 9.1 Diuretic compounds in *Taraxacum officinale* and their additional properties

S No.	Diuretic compound	Other activities
1	Ascorbic acid	Nutrient
2	Caffeic acid	Anti-aggregant, anti-inflammatory, anti-anxiolytic
3	Calcium	Nutrient
4	Chlorogenic acid	Antioxidant, cardioprotective, anti-inflammatory
5	Isoquercitrin	Antioxidant, hypotensive, anti-inflammatory
6	Luteolin	Anti-inflammatory, antioxidant, hypocholesterolemic, vasodilator
7	Magnesium	Nutrient
8	Mannitol	Antioxidant, anti-inflammatory
9	Potassium	Nutrient

diuretic action of dandelion might be expected due to several compounds by means of various diuretic and saluretic pathways (Table 9.1).

9.4.3 Hepatoprotective Effect

Dandelion (*T. officinale*) has been generally utilized in the treatment of the various liver issues. Shi et al. (2009) conducted investigation to survey the adequacy of dandelion root water–ethanol extract (DWE) in carbon tetrachloride (CCl4)-initiated hepatic fibrosis. Expanded hepatic collagen deposition due to CCl4-induced hepatotoxicity has shown the development of liver fibrosis. The Dandelion Water Extract (DWE) treatment has incited withdrawal of collagen stores in necrotic zones and the inversion of hepatic fibrosis. Furthermore, the examination proposes that polyphenolic acid, chlorogenic acid, etc. have been recognized in DWE, which has inhibitory potential on CCl4-instigated liver fibrosis in rodents by inactivating hematopoietic stem cells (HSCs) (Shi et al. 2009). *T. officinale* root has defensive activity against alcohol-prompted liver damage by lifting antioxidative properties and diminishing lipid peroxidation. Ethanol-prompted hepatic damage is portrayed by hepatic marker catalysts, for example, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and lactic dehydrogenase (LDH). The elevation of these proteins in serum proposes hepatocytic damage (Kasdallah et al. 2007). Irreversible liver damage prompted by the consumption ethanol is apparently connected with oxidative stress by means of improved lipid peroxidation and ROS creation. The aqueous extract from the tissues of *T. officinale* is considered as a potentially helpful radical scavenger for a large group of radicals. It is assumed that the cancer-preventing activity of the aqueous extract of *T. officinale* could be in charge of the amelioration of oxidative stress. In this way, the development of dietary supplementation utilizing *T. officinale* could be supportive to secure against alcoholic liver damage interceded by oxidative stress.

9.4.4 Hypolipidemic Activity

Dandelion (*T. officinale*) has the capacity to reduce lipid levels and lipoproteins in the blood. Especially, leaf extracts and unrefined powdered tissues of dandelion diminished triglyceride collection in adipocytes to a more noteworthy degree than that of the extract from the root. Treatment with dandelion root and leaf absolutely changed plasma and lipid profiles in cholesterol-sustained rabbits, and consequently may have potential hypolipidemic and cancer prevention activity (Choi et al. 2010).

9.4.5 Cardiovascular Activity

Dandelion is helpful in averting hypercholesterolemia and atherosclerosis, and diminishing risk factors for coronary conduit sickness. In the human body, abnormal amounts of triglycerides in the circulation system have been connected to atherosclerosis, and, by expansion, the danger of coronary illness and stroke. Raised cholesterol level is a hazard factor for coronary illness. The development of plaque in the course may prompt narrowing (hypertension) or complete blockage (heart attack) of the vessel (Karantonis et al. 2006). It is generally acknowledged that decrease in plasma HDL is a hazard factor for developing atherosclerosis. The dandelion leaf supplemented-diet expanded the centralizations of serum HDL-c when it is contrasted, and the cholesterol-rich eating routine and the convergences of serum LDL-c were diminished (Jinju et al. 2008).

9.4.6 Probiotic Activity

Fluid root concentrates of *T. officinale* Weber were tried for their development animating movement of 14 unique strains of bifidobacteria. The development of some strains was essentially upgraded in the medium containing dandelion root separately, while just two strains grew marginally less serious in this medium contrasted with the control. The remaining six strains showed proportionate development in the two media.

Overall, 1–48% of utilization of oligofructans from dandelion has been revealed before and after incubation in all bifidobacterial cultures (Trojanova et al. 2004).

9.4.7 Neuroprotective Activity

Oxidative stress–mediated neuron damage is considered an important factor to the pathogenesis and development of neurodegenerative diseases. *T. officinale* has been reported to possess antioxidant activities. However, its protective ability and underlying molecular mechanisms have not been elucidated yet. However, the neuroprotective activity of ethanol extracts of this plant on glutamate-induced oxidative stress in HT22 cells has been demonstrated by Huang S and his coworkers

in 2018. Both cell viability and reactive oxygen species (ROS) assays showed that its ethanolic extracts effectively attenuated glutamate-induced cytotoxicity and ROS generation. Ethanolic extracts also increased the expression of heme oxygenase-1 (HO-1) and promoted the nuclear translocation of nuclear factor erythroid 2-related factor-2 (Nrf2). The inhibitory effects of ethanolic extracts on glutamate-stimulated cell toxicity and ROS production were partially reversed by tin protoporphyrin (SnPP), an HO-1 activity inhibitor. Taken together, these results demonstrate that ethanolic extracts can protect HT22 cells against glutamate-induced oxidative damage by inducing the Nrf2/HO-1 pathways (Huang et al. 2018).

9.4.8 Antibacterial Activity

Dandelion (*T. officinale*) shows antibacterial activity, that is, it destroys or suppresses the growth of bacteria. Oligosaccharides were derived from dandelion by hydrolysis with hydrogen peroxide (H_2O_2). The extraction conditions were optimized using the response surface methodology, and the antibacterial activity of dandelion-derived oligosaccharides (DOs) was determined (Li et al. 2014).

The antimicrobial viability of rough and dialyzed extracts from the dandelion root was tried against three Gram-positive (*S. aureus*, methicillin-resistant *Staphylococcus aureus* [MRSA], and *B. cereus*) and two Gram-negative (*E. coli* and *S. Typhimurium*) bacterial strains. The hexane rough concentrate (DRE1) exhibited antimicrobial movement against *B. cereus* (MIC = 1000 μg/mL), while the DCM extricate (DRE2) was dynamic against *S. aureus* and MRSA (MICs = 1000 μg/mL). DRE3 showed the most grounded antimicrobial action, in relation to unrefined dandelion removes, and was dynamic against each of the three Gram-positive to resist MIC = 500 μg/mL. An investigation by Sengul et al. (2009) examined the zonal restraint of rough methanol and water Soxhlet extract from the aerial parts of dandelion against 32 bacterial strains. The most grounded movement was found in the methanol separate, which was active (MICs = 300 μg/mL) against 10 bacterial strains especially against *B. cereus* (6 cm range). Likewise, Sengul et al. (2009) credited the antimicrobial action of the methanol extract to the presence of phenolics and in this manner connected this to its cancer prevention agent movement. Another study by López et al. (2013) announced that a fluid methanol (90% v/v) extract of dandelion blossoms exhibited no restraint of bacterial development against *S. aureus* and *E. coli*. In this examination, DRE3 was obtained from a methanol extract of dandelion root material and was observed to be active (MIC = 500 μg/mL) against *B. cereus* and *S. aureus*, although no hindrance to *E. coli* development was reported. Based on the action shown by DRE3, further fractionation of this unrefined concentrate was completed utilizing NP flash chromatography. The methanol hydrophobic rough extract (DRE3) revealed the most antimicrobial action against *S. aureus*, MRSA, and *B. cereus* strains (250–500 μg/mL), while no movement was seen against *E. coli* and *S. typhimurium*.

9.4.9 Anti-Inflammatory Activity

Inflammation is an intricate response of the host against several injuries. This reaction generally occurs by the means of immune cells like monocytes and macrophages, which stimulate inflammatory mediators such as nitric oxide (NO), prostaglandin E_2 (PGE_2), and tumor necrosis factor (TNF)-a (Munhoz et al. 2008). *T. officinale* has been used since earlier times as a herbal medicine to treat various medical issues, along with inflammatory disorder (Jeon et al. 2008). The anti-inflammatory effects of *T. officinale* extracts have been stated in both in vitro and animal models (Kim et al. 2000). Among the identified constituents in HPLC evaluation, protocatechuic acid (Jiang et al. 2015), caffeic acid (Kim et al. 2014), chlorogenic acid (Hebeda et al. 2011), and ferulic acid have showed anti-inflammatory activity inside the endothelial system. New research of Hu et al. suggested that aqueous extracts of *T. officinale* suppressed both TNF-α and Intercellular Adhesion Molecule-1 (ICAM-1) expression in lipopolysaccharide (LPS)-stimulated microvascular endothelial cells of mammary glands in rats. It is also shown that the anti-inflammatory effect of the TO methanolic extract on human endothelial cells is mediated via reduction of Vascular Cellular Adhesion Molecule-1 (VCAM-1) and pro-inflammatory cytokine expression. As endothelial VCAM-1 is considered as an important factor of mononuclear cell (monocytes and a few T lymphocytes) adhesion, lowered VCAM-1 expression considerably explains the inhibited monocyte adhesion to LPS-stimulated endothelial cells.

Overproduction of NO, via inducible NO Synthase (NOS), is responsible for the synthesis of NO from l-arginine, and is intently linked with inflammatory diseases, as well as the evolution of atherosclerosis and cancer (Kolb and Kolb 1992). Cyclooxygenase (COX)-2 is the enzyme that helps in the production of PGE_2 from arachidonic acid. The abnormally high levels and overexpression of COX-2 enzyme is determined in numerous premalignant and malignant tissues (Na and Surh 2006). The inflammatory phenomenon is also mediated via pro-inflammatory cytokines and chemokines, including interleukin (IL)-1, TNF-a, and IL-8, which are generated by activated macrophages. It has been reported that TNF-a plays an important role in the inflammatory processes (Yang et al. 1998). The expression of NOS, COX-2, and TNF-a is mediated through nuclear factor kappa B (NF-kb), which exists universally within the cytoplasm. This inflammatory transcription factor contains p50 and p65 subunits which are attached to an inhibitory protein, IkBa. In response to inflammatory stimuli brought about by bacterial endotoxin lipopolysaccharide (LPS), and IkBa is phosphorylated and secreted from NF-kB. The activated NF-kB subunits, p50 and p65, then transfer into the nucleus and upregulate inflammation-associated genes (Sha 1998). LPS stimulation can result in the activation of numerous intracellular signaling molecules. It has been shown that LPS can activate the Mitogen-Activated Protein Kinase (MAPK) (Anand et al. 2009) and NF-κB pathways in endothelial cells (Ghosh and Hayden 2008). These pathways are concerned in controlling the expression of adhesion molecules and pro-inflammatory cytokines. Western blot evaluation indicated that TO have no effect on LPS-induced MAPK activation, while immunofluorescence staining

showed that TO markedly suppresses LPS-precipitated NF-κB nuclear translocation. As NF-κB nuclear translocation is mediated by IκBα, the degradation of which is brought about by means of phosphorylation, TO treatment was linked with suppression of IκBα phosphorylation. This suggests that TO reduces the LPS-induced endothelial expression of VCAM-1 and pro-inflammatory cytokines by means of suppressing activation of the NF-κB pathways.

T. officinale was found to have acute anti-inflammatory activity by showing its dominant effect against cholecystokinin-induced acute pancreatitis in rats (Seo et al. 2005). The flavonoid compounds, luteolin and luteolin-7-O-glucoside, present in the ethyl acetate fraction of *T. officinale* inhibit the synthesis of nitric oxide (NO) and prostaglandin E_2 in LPS-activated RAW264.7 macrophage cells, which occurs due to the inhibition of inducible nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2) (Hu and Kitts 2004). However, in primary cultures of rat astrocytes activated with LPS and TNF-a inducing substance P, *T. officinale* considerably inhibits production of TNF-a by inhibiting IL-1 secretion, indicating an anti-inflammatory property of *T. officinale* in the central nervous system (CNS) (Kim et al. 2000). It was reported that pretreatment with *T. officinale* extracts protect against LPS-induced acute lung injury in mice (Liu et al. 2010).

9.4.10 Antidiabetic Activity

Type 2 diabetes is the metabolic disorder which is spread over wide range of developed and developing countries. In 2007, it was reported that 3.5 million deaths occurred due to diabetes (Das and Rai 2008). The world is dealing with a massive medical and financial burden because of the rise in the occurrence of diabetes. It is calculated that approximately 382 million people in the world is suffering from type 2 diabetes today, and it is anticipated that by 2035 this number would rise by more than 200 million if precautionary measures are not taken (Whiting et al. 2011). The huge increase in the economic burden of type 2 diabetes has led to look for replacement of expensive medicines with the affordable ones. Dandelion gives a compelling profile of bioactive components with capability of antidiabetic properties. These bioactive components are sesquiterpene lactones, triterpenes/phytosterols (taraxasterol), phenols, flavonoids, and phenolic acids (Schütz et al. 2006). Dandelion is also the abundant source of the vitamins (A, C, D, E, and B), inositol, lecithin, etc., and minerals such as iron, magnesium, sodium, calcium, silicon, copper, phosphorus, zinc, and manganese (Ata et al. 2011). The movement of some of these ions (e.g., calcium ions in beta cells) may help to trigger insulin exocytosis (Komatsu et al. 1997).

Insulin resistance occurs in various tissues including liver, adipose tissues, and muscle cells and is the primary reason for hyperglycemia and a characteristic in pathogenesis of T2D (Hamden et al. 2008). There is one more widely known mechanism that has an impact on glucose homeostasis and that is oxidative stress, which is drifted by means of auto-oxidation and protein glycation (Giugliano et al. 1996). This process may increase the synthesis of lipid peroxide, which in turn

decreases the antioxidative protection (Seo et al. 2005), as a consequence supporting the development of β-cell dysfunction. β-cell dysfunction impairs secretion of insulin due to glucotoxicity and lipotoxicity, which negatively influences the conversion of proinsulin to insulin. Hussain et al. (2004) reported that dandelion extracts could stimulate the secretion of insulin from pancreatic β-cells, which consequently opposes the influence of hyperglycemia. He further reported that rat insulinoma cells (INS-1E cells) have insulin activity. Dried ethanolic extract (40 μg/ml) of *T. officinale* was given to cells in presence of high glucose (6.0 mM), using glibenclamide (an anti-diabetic drug) as a control. The authors reported that an extensive insulin secretion occurred with the aid of INS-1E cells compared to ordinary glucose (3.0 mM). It has been revealed that chicory acid (CRA) also increase the uptake of glucose in muscle cells due to the stimulation of insulin secretion in the pancreas (Tousch et al. 2008). Dandelion, when administered as a 9.7% herbal preparation of ethanolic extract, has anti-hyperglycemic property in non-overweight diabetic mice (Petlevski et al. 2003). Moreover, CRA and TS (Taraxasterol) blocks α-glucosidase and α-amylase, stopping the digestion of complex carbohydrates consisting of starch and as a result contributing to the anti-hyperglycemic effect (Schütz et al. 2006).

The important factor in T2D is the impairment of insulin secretion and insulin sensitivity that leads to rise of blood sugar levels (hyperglycemia) and T2D, which can later lead to the development of vascular diseases (Resnick and Howard 2002). Since T2D is a huge economic and social burden and an epidemic phenomenon, many countries are becoming more dependent on antidiabetic medicines (Onal et al. 2005). The mature root of dandelion contains 40% of inulin which is a mixture of complex carbohydrates called as fructo-oligosaccharides (FOS). Intake of FOS benefits bifidobacteria that destroy pathogens in the gastrointestinal tract (Mir et al. 2015). FOS stimulates the immune system due to increase in the mineral absorption and thus inhibits abnormal cell growth. This complex carbohydrate helps to maintain constant blood sugar levels. According to Amin et al. (2015), it lowers hyperglycemia when used in high levels of water extract. Chlorogenic acid (CGA) has been found to be the potential compound for preventing obesity and inflammation. It also have effect on insulin secretion and sensitivity, making it an alternative for use as a future antidiabetic drugs (Xiao et al. 2013).

9.4.11 Antidepressant Activity

Depression is a wide spread disorder that is often persistent and is associated with physical and psychosocial problems including suicide (Dos et al. 2016). Now-a-days, the treatment regimens which are used for the control of depression show a number of adverse effects and have a negative impact on patient health (Polyakova et al. 2015). Therefore, we need to develop alternative therapeutics with better efficacy and lesser adverse effects. Natural products have been used since ancient times for the alleviation of human ailments and they have been used to cure many diseases including depression (Mhalla et al. 2018).

Recent studies have shown that *T. officinale* exhibit antidepressant activity (Li et al. 2014). It was confirmed by Tail Suspension Test (TST) that the hydromethanolic extract of *T. officinale* possesses antidepressant activity, showing that the extract can considerably alleviate the TST-induced immobility and the results had been similar to the positive control bupropion that is an antidepressant. It has also been suggested that stresses such as the TST in mice results in human depression-like situation and stimulates corticosterone production, which in turn results in a series of endocrine events (Van Donkelaar et al. 2014). The hydromethanolic extract of *T. officinale* exhibit antidepressant activity by reducing corticosterone levels and by increasing the adrenaline, noradrenaline, and dopamine levels. Further, it has been found that this extract can upregulate the expression of the brain-derived neurotrophic factor (Bdnf), which is associated with decreased expression of mitogen-activated protein kinase phosphatase-1 (Mkp-1), and thus exhibit protective effects in TST-stressed mice (Kondo et al. 2015). The active constituents of *T. officinale* responsible for antidepressant activity are identified as isoetin, hesperidin, naringenin, kaempferol, sinapic, and gallic acid. Thus, *T. officinale* might be beneficial in the control and management of depression.

9.4.12 Anti-Fatigue and Immunostimulatory Activity

T. officinale has been used to enhance energy levels in Korean herbal medicine. The anti-fatigue and immune-enhancing effects of *T. officinale* were examined in mice by performing Forced Swimming Test (FST) and in vitro via use of peritoneal macrophages, respectively. After daily oral intake of *T. officinale*, blood biochemical parameters related to fatigue were measured after the FST. FST immobility time was significantly decreased in the *T. officinale*-treated group (100 mg/kg) and also increased glucose levels, acting as an energy source. Swimming is known to initiate changes in biochemical parameters of blood (Lee et al. 2012). Blood urea nitrogen (BUN), creatine kinase (CK), lactic dehydrogenase (LDH), glucose, and albumin are biochemical parameters of blood related to fatigue. The BUN test is often used to assess renal function. The BUN level decreased when *T. officinale* was administered to mice. CK and LDH are known to be specific indicators of muscle damage. LDH catalyzes the interconversion of pyruvate and lactate; consequently the level of LDH increases rapidly after exercise. It was found that LDH levels were reduced after *T. officinale* treatment whereas CK levels does not change. After the FST, glucose levels had been considerably increased by the oral intake of *T. officinale*. Thus, these results suggest that *T. officinale* might be useful as an energy source.

There are various functions of macrophages including tissue remodeling during embryogenesis, wound repair, removal of broken or senescent cells subsequent to infection or injury, hematopoiesis, and homeostasis. One more function of macrophages is to prevent microbial invasion and to recognize and kill tumor cells. In vitro tests were carried out in mouse peritoneal macrophages to illustrate the immune-enhancing effect of *T. officinale*. Cytokines such as IL-12 and TNF-α are produced by macrophages, which enhance cellular-mediated immunity

(Kim et al. 2011). TNF-α production and mRNA expression were upregulated by *T. officinale* in combination with recombinant Interferon gamma (rIFN-γ) treatment in mouse peritoneal macrophages. *T. officinale* treatment may additionally enable the induction of cellular-mediated immunity and restrict inflammatory reactions in a severe inflammatory state. We advise that IL-10 is a key cytokine within the *T. officinale*-mediated law of immune function in murine macrophages. Furthermore, *T. officinale* extended TNF-α, interleukin IL-12p70, and IL-10 stages, and NO production in primary cultured peritoneal macrophages. It can be concluded that *T. officinale* has the capability to improve immune effects.

9.4.13 Anticancer Activity

As it is well known that cancer is the disease of stem cell (Zhang et al. 2012), therefore cancer stem cells (CSCs) have the potential for countless proliferation, and play an important role in case of carcinogenesis, metastasis, recurrence, and drug resistance. Sox2 is one of the gene that retains self-complacency of embryonic stem cells; is related to the differentiation capacity of these cells; and is expressed abnormally in several human tumors which include ovarian cancer, pancreatic cancers, breast cancer, lung squamous cell carcinoma, and gastrointestinal tumors (Yang et al. 2014). Sox2 plays an important function in breast carcinogenesis and excessive expression may incite metastatic potential (Lengerke et al. 2011). Therefore, goal therapy of CSCs is very essential in cancer control and management.

Dandelion (*T. officinale*) is well known as a folk medication as anticancer. The crude aqueous extract of dandelion leaf has been found to decrease the growth of MCF-7/AZ breast cancers cells, whereas the aqueous extracts of dandelion flower and root had no impact on its growth. Moreover, root extract blocked invasion of MCF7/AZ while dandelion leaf extract was found to block the invasion of LNCaP prostate cancers cells (Sigstedt et al. 2008). Ethanolic extract of *T. officinale* leaves have been stated as immunostimulatory agent for lowering side effects of doxorubicin in Sprague Dawley rats (Kasianingsih et al. 2011). Chatterjee et al. reported the potency of dandelion root extract in causing apoptosis in drug-resistant human melanoma cells, without noxious effect to healthy cells. For human primary culture cervical cancer stem cells (CCSCs), it has been shown that TO is effective in causing apoptosis, initiating RARß2 gene expression and suppressing Sox2 expression. Hata et al. found that upon screening of different compounds from wild flora, *T. officinale* was found to be the powerful inducer of differentiation in mouse melanoma cells. Moreover, this group of coworkers also located that one constituent of Chinese dandelion, Lupeol-a triterpene, stimulated melanogenesis and reduced cellular proliferation in mouse melanoma (Hata et al. 2000). This triterpene is considered as cytostatic and not cytotoxic.

T. officinale extract was found to treat Hep G2 human hepatoma cells and was discovered to lessen cellular viability and initiate cytotoxicity via interleukin-α and TNF-α (Koo et al. 2004). Phytochemicals in *T. officinale* encompass sesquiterpene lactones, triterpenoids, tannins, alkaloids, flavonoids, steroids, and phenolic acids

(Kim and Lee 2007). Oleic acid has additionally been discovered inside the stem of *T. officinale* demonstrating antiproliferative activity (Laszcyk et al., 2009). The flavonoid luteolin is found to be the effective anticancer constituent of *T. officinale* (Cheng et al. 2005). Luteolin kills cancer cells through initiation of apoptotic cellular death in various cell types.

Cytotoxicity is an important aspect of the anticancer activity of a therapeutic agent; however apoptosis is a desired mechanism of action of such agents. *T. officinale* is found to have antioxidant properties as well. This property additionally plays a crucial role in scavenging reactive materials that would otherwise be the reason for causing number of diseases including cancer. Apoptosis is critical mechanism for the preservation of cellular homeostasis by means of regulating cell division and cellular death (Yan et al. 2008). The system is mediated via activation of certain conservative intracellular pathways resulting in the exhibition of weird characteristics by apoptosed cells such as morphological modifications and DNA fragmentation. Some research have shown that apoptosis is related to cancer, as most cancers cells are characterized by means of reduced apoptosis. Hence, activation of apoptotic pathways is taken into consideration as an important mechanism taken up by most cytotoxic drugs to damage cancer cells (Xu et al. 2009). The compound oleanolic acid which is known to block cell proliferation and result in apoptosis has been found within the stem of *T. officinale* (Li et al. 2013). This compound has same structure as that of ursolic acid with moderate variations within the substituents on carbon 20. Consequently, the presence of oleanolic and taraxanic acid are considered to be responsible for the growth inhibitory and apoptotic outcomes of the *T. officinale* extracts.

9.5 Phytochemistry of *T. officinale*

T. officinale, a herbaceous perpetual plant of the family Asteraceae, is observed to have numerous medicinal properties including antidiabetic, antimicrobial, diuretic, carminative, hepatoprotective, antioxidant, and anticancer features. These properties have been ascribed to the extensive number of bioactive constituents in their tissues, including terpenes, flavonoids, and phenolic compounds, which are referenced as in charge of the therapeutic action of the plant (Table 9.2).

9.5.1 Constituents of Dandelion Roots

Various sesquiterpenes like taraxacolide-O-glucopyranoside, the guaianolides 11,13-dihydrolactucin and ixerin D, eudesmanolides, tetrahydroridentin B and three germacranolide esters, taraxinic acid glucopyranoside, including 11,13-dihydro-derivative and ainslioside have been documented in *T. officinale* WEBER root extracts (Hinsel et al. 1980; Kisiel and Barszcz 2000).

Furthermore taraxacoside, an acylated-butyrolactone glycocide have been isolated from *Taraxacum officinale* roots (Rauwald and Huang 1985). In addition,

Table 9.2 Phenolic constituents of dandelion tissue

Compound	Plant tissue		
	Leaf	Flower	Root
Luteolin −7-glucoside	+	+	−
Luteolin −7-diglucoside	+	+	−
Luteolin −7-diglucoside	+	+	−
Free luteolin	−	+	−
Free chrysoeriol	−	+	−
Chicoric acid	++	+	++
Mono caffeoyl tartaric acid	+	+	+
Chlorogenic acid	+	+	+
Cichoriin	+	−	−
Aesculin	+	−	−

traxacum species are known to have matricarin-type guaianolides (Kisiel and Michalska 2005).

Dandelion roots offer various phytoconstituents including various phytosterols such as taraxasterol, their estates and their 16-hydroxy derivatives arnidol and faradiol; triterpenes and amyrin, citosterol, citosterol-D-glucopyranoside and stigma sterol (Table 9.3) (Burrows and Simpson 1938; Hinsel et al. 1980; Akashi et al. 1994).

Dandelion roots have identified numerous phenolic compounds, for example, caffeic acid, chicoric acid along with its various isomers, 4-caffeoylquinic acid, p-coumaric acid, mono caffeoyl tartaric acid, chlorogenic acid, ferulic acid, vanillic acid, p-hydroxybenzoic acid, protocatechuic acid, syringic and p-hydroxy phenyl acetic acid. Furthermore, presence of many coumarins including scopoletin, esculetin, and umbelliferone have been established in *T. officinale* roots (Clifford et al. 1987; Wolbis et al. 1993; Williams et al. 1996). In addition to secondary metabolites present in taraxacum roots, it also contains inulin in an appreciable amount. Inulin content (storing carbohydrate) varies due to seasonal changes, being high in autumn (40%) and low in spring (2%) (Bisset et al. 1994).

9.5.2 Constituents of *T. officinale* Leaves

Analogous to dandelion roots, *T. officinale* leaves are also known to have bitter components, that is, sesquiterpenes like 11,13-dihydrotaraxinic-acid α-D-glucopyranoside and taraxinic acid α-D-glucopyranoside. The bitter taste of dandelion leaves may also be attributed to the presence of sitosterol and *p*-hydroxyphenylacetic acid (Kuusi et al. 1985). The leaves of *Taraxacum* are known to have higher concentration of polyphenolic compounds. Williams et al. (1996) have measured the concentration of cinnamic acid in both dandelion roots and leaves, which was obtained to be 1.2 mg/g and 16 mg/g respectively. Certain phenolic groups are present in abundance in leaves and flowers of dandelion as hydroxycinnamic acid derivatives, specifically caffeic acid esters such as

Table 9.3 Compounds in *Taraxacum officinale* with thei documented pharmacological activity

Compound	Nature of compound	Isolated from	Pharmacological activity	Used	References
Quininic acid	Phenolic	Root and leaf	Hypolipidemic and antioxidant hepatic disorders, diuretic, anti-rheumatic	Whole extract	Williams et al. (1996), Kim et al. (2008)
Quinic acid	Phenolic	Roots, flower, leaves and stem	Type i2iDiabetes (T2D), hepatic disorders	Ethanolic extract	Mingarro et al. (2015), Kenny et al. (2015), Fraisse et al. (2011), Choi et al. (2010), I Schütz et al. (2006)
Quercetin triglycoside	Flavone glycoside	Leaves and root	Treatment of gout	Whole extract	AbdAziz et al. (2011), Kong et al. 2001)
Quercetin pentoside	Flavonoids	Root and stem	Antioxidant	Methanolic extract	Clifford et al. (2003), Hu and Kitts (2005), Jeon et al. (2008)
11,13-Dihydrolactucin	Terpene	Root	Antidiuretic	Hydroethanolic extract	Kisiel and Barszcz (2000)
Ixerin D	β-D glucopyranose	Root	Choleretic anti-diuretic and anti-inflammatory	Ethanolic extract	Williams et al. (1996)
Ainslioside	Flavone glycoside	Leaves and roots	Against herbivore attack	Secondary metabolite	Schütz et al. (2006)
Taraxacoside	Glycoside	Root	Anti-inflammatory	Aqueous methanolic extract	
Taraxasterol	Triterpenoid	Root	Anti-cancer activity, Alzheimer's and parkinsonism prevention, Antiallergic, alpha-amylase inhibitory activity, antioxidant activity	Plant tissue culture	Sharma et al. (2009), Whang et al. (2011), Kumar et al. (2008), Jamshieed et al. (2010)
Faradiol	Triterpenoid	Root	Appetite stimulating and laxative property gall bladder disorder, digestive complaints	Root tincture	Blumenthal et al. (2000)

Cinnamic acid	Phenolic	Flowers and leaves	Anti-rheumatic and anti-inflammatory	Methanolic extract	Bradley (1992), Gonzalez et al. (2012)
Luteolin	Flavonoid	Flower and leaver	Anticancer and anti-inflammatory activity	Whole extract	Cheng et al. (2005)
Taraxinic acid	Phenolic	Flowers and leaves	Antiproliferative activity	Whole extract	Li et al. (2013)
Chlorogenic acid	Phenolic	Root	Antiproliferative activity	Whole extract	Hebeda et al. (2011)
Chicoric acid	Phenolic	Root	Antidiabetic activity	Ethanolic extract	Tousch et al. (2008)
Naringenin	Flavonoid	Leaves and flowers	Antidepressant activity	Hydro-methanolic extract	Van Donkelaar et al. (2014)

dicaffeoyltartaric (chicoric acid), chlorogenic, and monocaffeoyltartaric acids (Williams et al. 1996; Budzianowski 1999). *Taraxacum* leaves and flower extracts bring forth several flavonoid glycosides such as isorhamnetin 3-*O*-glucoside, luteolin 7-*O*-glucoside, quercetin 7-*O*-glucoside, apigenin 7-*O*-glucoside, and luteolin 7-*O*-rutinoside extract (Wolbis and Krolikowska 1985; Wolbis et al. 1993; Williams et al. 1996; Kristo et al. 2002). Schuetz et al. (2006) in another study has demonstrated various di- and triglycosylated flavonoids in dandelion herb and root extract. In addition to flavonoids, some coumarins namely aesculin and cichoriin have been shown to be present in leaf extract of dandelion extract (Williams et al. 1996; Budzianowski 1999). Potassium content of leaves and stem (4.89% and 7.73% dry matter, respectively) have been calculated as well, justifying the diuretic properties of dandelion tea (Hook et al. 1993; Wilman and Riley 1993; Wilman and Derrick 1994). Luteolin 7-glucoside and two luteolin 7-diglucoside glycosides have been isolated from dandelion leaves and flowers, and also two flavonoid components chrysoeriol and luteolin were obtained in free state for the very first time in dandelion flower tissue, although free luteolin has been reported earlier in a collective leaf and flower extract of Polish dandelions (Wolbis et al. 1993; Power and Browning 1912). In addition to the presence of these flavonoids, many carotenoids are also surprisingly present. Caffeic acid esters were seen to be major constituent of dandelion leaf, flower, and root extracts. Table 9.2 shows a comparison of the phenolic constituents of dandelion tissues. Coumarins have been detected in leaf only, and no flavonoids have been reported in dandelion roots (Racz et al. 1974). Grieb Von and Duqunois (1960) have reported that since dandelion root and leaves are high in potassium content, it might be present in taraxacum species in combination with cinnamic acid (being adequately present in dandelion species); alike sesquiterpene lactones which are present in dandelion roots, linked to glycosides. Taraxacoside was reported for the first time as an acylating acidic compound in sugar ester (Rauwald and Huang 1984). Other documented compounds comprise taraxasterol from the root latex (Power and Browning 1912).

9.5.3 Constituents of *T. officinale* Flowers

The dandelion flowers are comprised of b-sitosterol, carotenoids, for example, lutein epoxide, triterpenes (b-amyrin, faradiol, arnidiol) (De Smet 1993; Melendez et al. 2006) and flavonoids like luteolin 7-O-glucoside and luteolin. Yellow oil had been extracted from the flowers of dandelion via hydro-distillation, and GCMS techniques have revealed many compounds from *T. officinale* like straight chain and branched aliphatic hydrocarbons, alkylated benzenes, ketones, alcohols, and esters (Hu and Kitts 2003; Hu and Kitts 2005).

The phytochemistry of *T. officinale* may be summarized as a bunch of phytoconstituents including triterpenes, sesquiterpene lactones, fatty acids, carotenoids, volatile oils, tannins, carbohydrates, phenolic acids, flavonoids, minerals, phytosterols, sugars, choline, vitamins, micronutrients, mucilage, pectin,

calcium, inositol, fats, gluten, proteins, and resin (Blumenthal et al. 2000; Williams et al. 1996).

Some of the potent bioactive compounds present in *T. officinale* are summarized in Fig. 9.1.

9.6 Conclusion

T. officinale significantly possess wide variety of secondary metabolites, thus representing useful source of bioactive compounds and preparations with health encouraging effects like antioxidant, diuretic, hypolipidemic, prebiotic, neuroprotective, antibacterial, anti-inflammatory, and antidiabetic. The diverse effects of dandelion are attributed to the presence of various triterpenes, sesquiterpenes, fatty acids, and phytosterols. The pharmacological investigations confirmed the empirical traditional application of dandelion in humans for the treatment of digestive disorders. Dandelion evaluated for phytochemical constituents had great potential to act as a source of useful drugs and ameliorate health condition of consumers due to the presence of various compounds that are indispensable for good health.

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Arctium lappa: A Review on Its Phytochemistry and Pharmacology

10

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Abstract

Arctium lappa (family, *Asteraceae*), commonly called Burdock, owing to its diverse volatile and nonvolatile metabolites is known for a variety of therapeutic and pharmacological effects. These secondary metabolites consist of phytosterols, terpenes/terpenoids, hydrocarbons, flavonoids, fatty acids, carboxylic derivatives, lignans, fatty acids, acetylenic compounds, polysaccharides, aldehydes, methoxypyrazines, carboxylic and fatty acids, monoterpenes, and sesquiterpenes. Burdock has also shown multifaceted pharmacological actions that include antidiabetic, antioxidant, hepatoprotective, anticancer, gastroprotective, antibacterial, antiallergic, antimicrobial, antiviral, and anti-inflammatory. This chapter aims to provide a comprehensive overview of the chemistry and biological activities of the secondary metabolites found in *A. lappa* and its species.

Keywords

Arctium lappa · Pharmacological properties · Phytochemistry · *Asteraceae*

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10.1 Introduction

Arctium lappa, commonly known as greater "burdock," "gobo," "edible burdock," or "beggar's button," is an Eurasian species belonging to family *Asteraceae*. The plant has been originally cultivated in Asia and Europe, but now it is being cultivated in different climates and countries as well. It has become an invasive weed of high-nitrogen-content soils that are mostly found in countries and regions like North America, Australia, and others regions. The plant is regarded as a nutritive and healthy food in Chinese societies. It has been used for its therapeutic value in countries of Europe, North America, and Asia for hundreds of years (Tabassum et al. 2018). The genus name has been derived from a Greek word "*arcteion*" which means "bear," alluding to the plant habitus which is characterized by marked hairiness. Among various species, *A. lappa* is most common and widespread, besides other species as *A. minus* and *A. tomentosum*. This shrub grows nearly up to 1 m in height and its young roots usually develop branches that can reach nearly 45–50 and 3–6 cm in depth and diameter, respectively. The shape of the roots is cylindrical, with slightly thin brown skin. The interior of the plant varies from white to yellowish-white that usually depends on the age of the plant (Barceloux 2008). The period from planting to reap varies from 8 to 12 months with a per hectare yield of 8–40 tons. Burdock roots, leaves, and seeds are used as therapeutic elements in traditional medicine, predominantly in the form of tea. Because of presence of a significant content of chlorogenic acid, the parts of plant have bitter and astringent taste (Chan et al. 2010; Burgmans et al. 1992).

In Chinese traditional medicine system, *A. lappa* is commonly known as "Niu Bang Zi" and is believed to be a healthy and nutritious food in Chinese societies. In folk medicine, seeds of *A. lappa* are crushed to form a combination that provides relief against common cold, tonsillitis, throat pain, measles, and arthritis. Burdock root is also used to treat ulcers, eczema, rheumatism, gout, psoriasis, and acne. In Chinese traditional system, dried burdock is used as a diaphoretic, diuretic, and blood-purifying agent. It is believed to purify blood by removing dangerous toxins. The extract from different parts of *A. lappa* has been considered beneficial for health, as it helps to improve the body's defense system and improves metabolic activities (Liu et al. 2012).

A. lappa and its species are characterized by hemicryptophyte plants that have erect taproot system and stout stems. The leaves are held sporadically as dentate, tomentose, alternate and cordate. The stem is usually strong, upright, grooved, usually branched, and reddish in color. Inflorescences (a cluster of flowers) is formed by corymbose or solitary conical-ovoid to orbicular capitula armed with involucres that are made up of bracts ending with curved apices. Receptacles are made up of many hard scales. Florets are hermaphrodite, white or purple in color. Pollination is mainly carried out by insects, generally belonging to Lepidoptera (The Scientific Foundation for Herbal Medicinal Products 2003). Figure 10.1 shows the photographic images of some species of Arctium at flowering stage, and Fig. 10.2 shows the photographic image of Arctium root.

Fig. 10.1 *A. lappa* species (Wang et al. 2019)

10.2 Phytochemistry of *A. lappa*

A. lappa has shown diverse pharmacological effects owing to the presence of diverse volatile and nonvolatile secondary metabolites like fatty acids, terpenes, flavonoids, lignans, acetylenic compounds, hydrocarbons, polysaccharides, phytosterols, terpenoids, aldehydes, carboxylic acids, fatty acids, monoterpenes, and sesquiterpenes (Swamy 2019). So far, over 200 nonvolatile compounds have been isolated and identified from this genus. With the advancement of technology different modern analytical techniques like high-performance liquid chromatograph (HPLC), thin layer chromatography (TLC), nuclear magnetic resonance (NMR),

Fig. 10.2 Burdock root (with copy right permission license number: 499428779638) (Chan et al. 2010)

mass spectrometry (MS), infrared (IR) spectrometry, etc., more active ingredients of this plant have been isolated over the last 10 years (Park et al. 2007). The details of chemical constituents, occurrence in different plant parts, viz. seeds, leaves, fruits, or roots, and the modern qualitative analytical techniques used for their determinations are briefly summarized in Table 10.1, whereas their detailed description is given in below section. The chemical structures of some of the nonvolatile compounds from *Arctium* and its species are shown in Fig. 10.3.

10.2.1 Lignans

Main bioactive lignans that are found in *A. lappa* include arctigenin (a dietary phytoestrogen) and its glycoside arctiin, which are mostly present in seeds, fruits, roots, and leaves (An et al. 2003; Ming et al. 2004; Liu et al. 2012). Apart from lignans, these plant parts are also rich in low levels of sesquilignans and dilignans. Lappaol A and B were the first sesquilignans isolated and characterized from the seeds of *A. lappa* (Ichihara et al. 1976). In the subsequent years more sesquilignans, namely Lappaol C, D, and E, and two dilignans, namely Lappaol F and H were structurally determined from the seeds of *A. lappa*. Boldizsár and colleagues in 2010 used simple high performance liquid chromatography analytical technique to

Table 10.1 Some of the nonvolatile compounds reported from *A. lappa*

S. no.	Compound name	Formula	Species	Plant origin/ part	Analytical method	References
Lignans						
1	Diarctigenin	$C_{42}H_{46}O_{12}$	*A. lappa*	Fruits, roots, seeds	IR/NMR/MS/TLC	
2	Arctin	$C_{27}H_{34}O_{11}$	*A. lappa, A. tomentosum*	Leaves fruits, roots, seeds	UV/IR/MS/NMR/HPLC/ LCMS/MALDI-QIT-TOF MS	Ferracane et al. (2010)
3	Arctigenin	$C_{12}H_{24}O_7$	*A. lappa, A. tomentosum*	Leaves fruits, roots, seeds	UV/MS/NMR/HPLC/LCMS/ MALDI-QIT-TOF MS/HRESI-MS	Boldizsár et al. (2010)
4	Arctigenin-4-O-α-D galactopranosyl-(1→6)-O-β-D-glucopyranoside	$C_{18}H_{32}O_{16}$	*A. lappa*	Fruits	NMR/UV/IR/ORD/HRESI-MS	
5	Arctigenin-4-O- β -Dapiofuranosyl-(1→6)-O-β-D-glucopyranoside	$C_{32}H_{42}O_{15}$	*A. lappa*	Fruits	NMR/UV/IR/ORD/HRESIMS	
6	7,8-Didehydroarctigenin	$C_{21}H_{22}O_5$	*A. lappa*	Fruits	HRFAB/EIMS/NMR	
7	Arctiidilactone	$C_{20}H_{20}O_8$	*A. lappa*	Fruits	NMR/UV/IR/ORD/HRESIMS	
8	Arctiiapolignan A	$C_{20}H_{28}O_{10}$	*A. lappa*	Fruits	NMR/UV/IR/ORD/HRESIMS	
9	Arctiisesquineolignan A	$C_{42}H_{52}O_{19}$	*A. lappa*	Fruits	NMR/UV/IR/ORD/HRESIMS	
10	Arctiisesquineolignan B	$C_{36}H_{46}O_{16}$	*A. lappa*	Fruits	UV/IR/HRESIMS/NMR	
11	Arctiiphenolglycoside A	$C_{19}H_{28}O_{13}$	*A. lappa*	Fruits	UV/IR/HRESIMS/NMR	
12	Arctignan A	$C_{30}H_{34}O_{10}$	*A. lappa*	Seeds	UV/MS/NMR/HPLC	
13	Arctignan B	$C_{30}H_{34}O_{10}$	*A. lappa*	Seeds	UV/MS/NMR/HPLC	
14	Arctignan C	$C_{30}H_{34}O_{10}$	*A. lappa*	Seeds	UV/MS/NMR/HPLC	
15	Arctignan D	$C_{30}H_{34}O_{10}$	*A. lappa*	Seeds	UV/MS/NMR/HPLC/LCMS/ MALDI-QIT-TOF MS	
16	Arctignan E	$C_{40}H_{44}O_{13}$	*A. lappa*	Seeds	UV/IR/MS/NMR/HPLC	Ferracane et al. (2010)

(continued)

Table 10.1 (continued)

S. no.	Compound name	Formula	Species	Plant origin/ part	Analytical method	References
17	Lappaol A	$C_{30}H_{32}O_9$	*A. lappa*, *A. tomentosum*	Seeds/fruits	TLC/UV/IR/MS/NMR/HPLC	Ferracane et al. (2010)
18	Syringaresinol	$C_{22}H_{26}O_8$	*A. lappa*	Roots	UV/IR/ESIMS/NMR	
19	(7S,8R)4,7,9,90-tetrahydroxy-3,30-dimethoxyl-70-oxo-8-40-oxyneolignan-4-O-β-D-glucopyranoside	$C_{26}H_{34}O_{13}$	*A. lappa*	Roots	IR/HR-ESIMS/NMR/CD	Yang et al. (2012)
20	(70S,80R,8S)-4,40,90-trihydroxy-3,30-dimethoxy-70,9-epoxylignan-7-oxo-4-O-b-D-glucopyranosyl-40-O-b-D-glucopyranoside	$C_{32}H_{42}O_{17}$	*A. lappa*	Roots	IR/HR-ESIMS/NMR/CD	Yang et al. (2012)
21	Arctiopicrin	$C_{19}H_{26}O_6$	*A. lappa*, *A. minus*	Leaves	TLC/NMR	Savina et al. (2006)
22	Dehydrovomifoliol	$C_{13}H_{18}O_3$	*A. lappa*	Leaves	NMR/HR-ESI-TOF-MS	Machado et al. (2012)
23	Loliolide	$C_{11}H_{16}O_3$	*A. lappa*	Leaves	NMR/HR-ESI-TOF-MS	Machado et al. (2012)
24	Dehydromelitensin-8-(4'-hydroxymethacrylate	$C_{15}H_{24}O_6$	*A. lappa*	Leaves	NMR/HR-ESI-TOF-MS	Machado et al. (2012)
25	Dehydromelitensin	$C_{15}H_{20}O_4$	*A. lappa*	Leaves	NMR/HR-ESI-TOF-MS	Machado et al. (2012)
26	Melitensin	$C_{15}H_{22}O_4$	*A. lappa*	Leaves	NMR/HR-ESI-TOF-MS	Machado et al. (2012)
27	3-α-Acetoxyhop-22(29)-ene	$C_{30}H_{49}O_2$	*A. lappa*	Leaves	NMR, IR and MS	Jeelani and Khuroo (2012)
28	3-α-Hydroxylanosta-5,15-diene	$C_{30}H_{50}O$	*A. lappa*	Leaves	NMR, IR and MS	Jeelani and Khuroo (2012)

Flavonoids						
1	Luteolin	$C_{25}H_{24}O_{12}$	*A. lappa*	Leaves roots	UPLC/LC-MS	Ferracane et al. (2010)
2	Rutin	$C_{27}H_{30}O_{16}$	*A. lappa*	Leaves	TLC/UPLC/LC-MS	Lou et al. (2010)
3	Quercitrin	$C_{21}H_{20}O_{11}$	*A. lappa*	Leaves roots	UPLC/LC-MS	Lou et al. (2010)
4	Quercetin	$C_{15}H_{10}O_7$	*A. lappa*	Leaves Roots	UPLC/LC/MS/MS/HRESIMS	Lou et al. (2010)
5	Quercetin 3-O-glucuronide	$C_{21}H_{18}O_{13}$	*A. lappa*	Roots	HPTLC/LC/ESI–MS/MS	Rajasekharan et al. (2015)
6	Quercetin 3-vicianoside	$C_{26}H_{28}O_{16}$	*A. lappa*	Roots	HPTLC/LC/ESI–MS/MS	Rajasekharan et al. (2015)
7	Quercetin rhamnoside	$C_{21}H_{20}O_{11}$	*A. lappa*	Roots	HPLC/LC/MS/MS	Ferracane et al. (2010)
Sterols						
1	β-Sitosterol	$C_{29}H_{50}O$	*A. lappa*	Seeds roots fruits	UV/IR/MS/NMR/HPLC	
2	Sitosterol-beta-D-glucopyranoside	$C_{35}H_{60}O_6$	*A. lappa*	Roots	IR/NMR/EI-MS	Miyazawa et al. (2005)
Fatty acids						
1	Methyl linolenate	$C_{19}H_{32}O_2$	*A. lappa*	Roots	IR/NMR/EI-MS/GCMS	Miyazawa et al. (2005)
2	Methyl oleate	$C_{19}H_{36}O_2$	*A. lappa*	Roots	IR/NMR/EI-MS/GCMS	Arctium et al. (2005)
3	Linolenic acid	$C_{18}H_{30}O_2$	*A. lappa*	Fruits	IR/NMR/EI-MS/GCMS	Kuo et al. (2012)

(continued)

Table 10.1 (continued)

S. no.	Compound name	Formula	Species	Plant origin/ part	Analytical method	References
4	Stearic acid	$C_{17}H_{35}CO_2H$	*A. lappa*	Fruits	IR/NMR/EI-MS	Arctium et al. (2005)
5	Arctinone-a	$C_{13}H_{10}O_2S_2$	*A. lappa*	Roots	UV/TLC/IR/NMR/MS	Washino et al. (1986)
6	Arctinone-b	$C_{13}H_{10}OS_2$	*A. lappa*	Roots	UV/TLC/IR/NMR/MS	Washino et al. (1986)
7	Arctinol-a	$C_{13}H_{12}O_2S_2$	*A. lappa*	Roots	UV/TLC/IR/NMR/MS	Washino et al. (1986)
8	Arctinol-b	$C_{13}H_{12}O_2S_2$	*A. lappa*	Roots	UV/TLC/IR/NMR/MS	Washino et al. (1986)
Carboxylic acids/quinic acids and derivatives						
1	Caffeic acid	$C_9H_8O_4$	*A. lappa*	Seeds leaves roots	TLC/HPLC/UPLC//LC/MC/ HRESI-MS	Ferracane et al. (2010)
2	Chlorogenic acid	$C_{16}H_{18}O_9$	*A. lappa*	Seeds leaves roots	TLC/HPLC/UPLC//LC/MC/ HRESI-MS	Liu et al. (2012)
3	p-Coumaric acid	$C_9H_8O_3$	*A. lappa*	Seeds leaves roots	UPLC/EI-MS	Lou et al. (2010)
4	Cynarin	$C_{25}H_{24}O_{12}$	*A. lappa*	Seeds leaves roots	UPLC/LC/MS	Ferracane et al. (2010)
Saccharides/polysaccharides						
1	Rhamnogalacturonan	$C_{117}H_{178}O_{101}$	*A. lappa*	Leaves roots	Chromatography/NMR/sugar analysis	Kato and Watanabe (1993)

2	Xylan	$(C_5H_8O_4)_n$	*A. lappa*	Leaves roots	Chromatography/NMR/sugar analysis	Kato and Watanabe (1993)
3	Galactose	$C_6H_{12}O_6$	*A. lappa*	Leaves roots fruits	Chromatography/NMR	Boldizsár et al. (2010)
4	Mannose	$C_6H_{12}O_6$	*A. lappa*	Roots leaves	NMR	Carlotto et al. (2016)
5	Arabinose	$C_5H_{10}O_5$	*A. lappa*	Roots leaves fruits	UV/NMR//HPLC/GCMS	Carlotto et al. (2016)
6	Fructose	$C_6H_{12}O_6$	*A. lappa*	Roots	HPLC-ELSD	
7	Sorbitol	$C_6H_{14}O_8$	*A. lappa*	Fruits	UV/NMR/HPLC/GCMS	Carlotto et al. (2016)
8	Mannitol	$C_6H_{14}O_8$	*A. lappa*	Fruits	UV/NMR/HPLC/GCMS	Boldizsár et al. (2010))
Others						
1	Crocin	$C_{44}H_{64}O_{24}$	*A. lappa*	Leaves	UPLC	Lou et al. (2010)

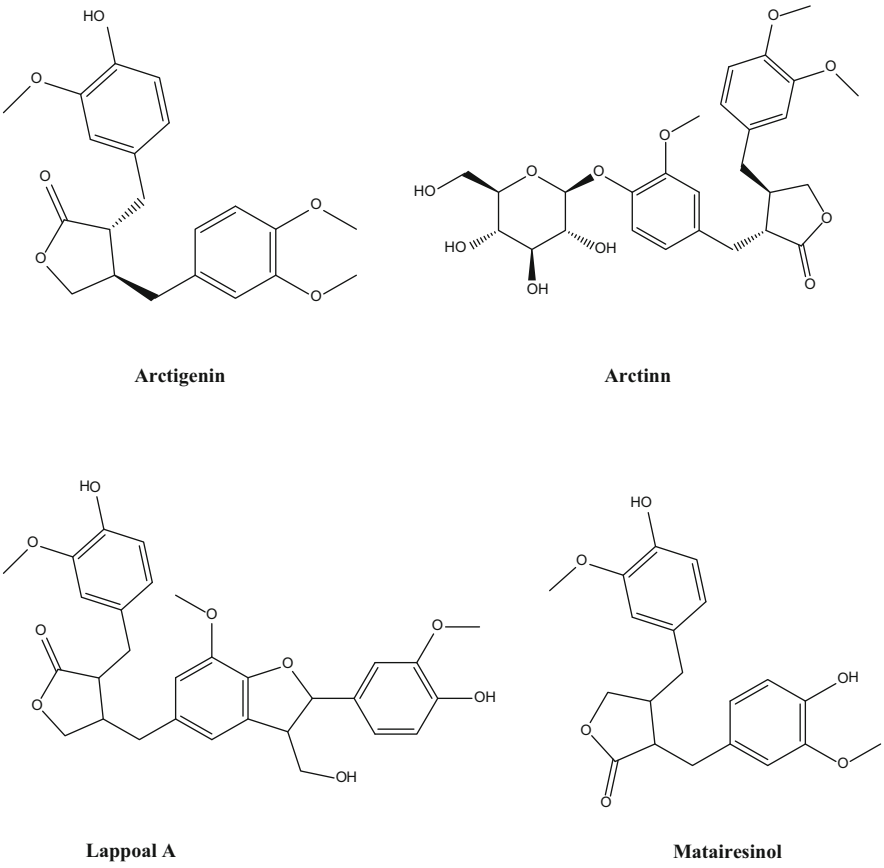


Fig. 10.3 Some volatile compounds reported in *A. lappa*

identify the presence of active constituent arctiin from the fruits of plant (Boldizsár et al. 2010). Using bioactivity-guided isolation and fractionation, Lappaol A, Lappaol C, Lappaol F, arctiin, and arctigenin E were isolated and later characterized from the ethanolic extract of *A. lappa* seeds (Ming et al. 2004). High-performance liquid chromatography (HPLC), mass spectrometry (MS), liquid chromatography (LC), and ultra-performance liquid chromatography (UPLC) quantitative analytical tools have been used to isolate and characterize arctigenin and arctiin in the roots, leaves, and seeds (Ferracane et al. 2010). A high-speed counter-current chromatography (HSCCC) was used to find the pure compound arctiin from the fruit extract of the plant. More than 49% of arctiin has been obtained by modern analytical techniques based on NMR and LC-MS (Wang et al. 2005).

10.2.2 Fatty Acids and Esters

Miyazawa and colleagues found 11 compounds in the methanolic extract of *A. lappa*. Among these, 10 belonged to fatty acid (Arctium et al. 2005). The compounds were identified as stearic acid, methyl stearate, methyl palmitate, palmitic acid, oleic acid, methyl linolenate, methyl oleate, linoleic acid, methyl linoleate, and linolenic acid. Iyazawa and colleagues in 2005 (Iyazawa et al. 2005) reported methyl palmitate, methyl linoleate, sitosterol-β-D-glucopyranoside, and methyl linolenate that showed an inhibitory effect against α-glucosidase. Later, Kuo et al. (2012) isolated and characterized methyl oleate, linolenic acid, and methyl-α-linolenate as the chief constituents from the *n*-hexane fraction of roots of the plant. The presence of palmitic acid, stearic acid, linoleic acid, and oleic acid has also been reported from the fruits of the plant (Boldizsár et al. 2010).

10.2.3 Acetylenic Compounds

Washino and colleagues in 1986 (Washino et al. 1986), identified and characterized 9 sulfur-containing acetylenic compounds, namely, arctinone-a & b, arctinol-a & b, arctinal, arctic acid-b & c, arctinone-a acetate, and methyl arctate-b from the plant**.** On spectral and chemical analysis, these compounds were found to be the products of 5′-(1-propynyl)-2′,2-bimethyl-5-yl. Later, presence of few guaianolides linked with sulfur-containing acetylenic compounds, viz. lappaphen-a & b, lactone, dehydrocostus, and dehydrodihydrocostus lactone, were isolated and characterized from the acetone extracts of the plant root (Washino et al. 1986). The plant possesses several bioactive constituents having acetylenic linkages that have demonstrated antibacterial, antifungal, and anti-edematogenic activities (Maria et al. 2016).

10.2.4 Phytosterols

A study carried out by Ahangarpour and colleagues on *A. lappa,* reported a natural phytosterol, daucosterol from its seeds (Ahangarpour et al. 2017). Other species of the plant, viz. *A. tomentosum* was found to contain two steroids (β-sitosterol and daucosterol). Ming et al. (2004), using bioactivity guided fractionation technique isolated β-sitosterol and daucosterol from ethanolic seed extracts of *A. lappa*. Later in 2005, sitosterol-β-D-glucopyranoside was also isolated from the ethanolic extract of the plant (Miyazawa et al. 2005).

10.2.5 Polysaccharides

Ferracane et al. (2010) for the first time reported the presence of pectic polysaccharides in edible roots of *A. lappa*. After that Watanabe in 1993, and more recently Carlotto and colleagues in 2016, isolated several polysaccharides

like pectic substances; rhamnogalacturonan with neutral sugars; hemicellulose (xyloglucan, xylan, galactan, arabinan, and arabinogalactan); cellulose, arabinose, and galactose from cell walls and roots of *A. lappa*; and leaves and roots of *A. minus* (Kato and Watanabe 1993). Biologically active inulin type fructofuranans and other fructo-oligosaccharides were isolated from the roots of *A. lappa* but in small quantity (Kardošová et al. 2003). It has been observed that these water-soluble polysaccharides obtained from the plant significantly increase the dysregulation of pro-inflammatory cytokines TNF-α, IL-6 and IL1β, and anti-inflammatory cytokines IL-10 (Wang et al. 2019).

10.2.6 Derivatives of Caffeoylquinic Acid (Carboxylic Acids)

They are the main bioactive phenolic constituents of *Arctium* species and the high antioxidant potential is thought to be due to these compounds. The roots of *A. lappa* have been found to contain derivatives of caffeoylquinic acid, viz. 1-0-,5-O-dicaffeoylquinic acid (Yang et al. 2012). Both chlorogenic acid and caffeic acid are present in the skin of roots of the plant; however, the quantity of former is more (Chen et al. 2004). HPTLC technique has been used as qualitative chemical profiling tool to estimate chlorogenic acid in roots. It has been reported that caffeoylquinic acid and its derivatives exhibit diverse biological activities like reduction in diet-induced obesity through modulation of peroxisome proliferator-activated receptor alpha (PPARα) and liver X receptors alpha (LXRα) transcription (Huang et al. 2015) and anti-ulcerogenic activity (Lee et al. 2010).

10.2.7 Flavonoids

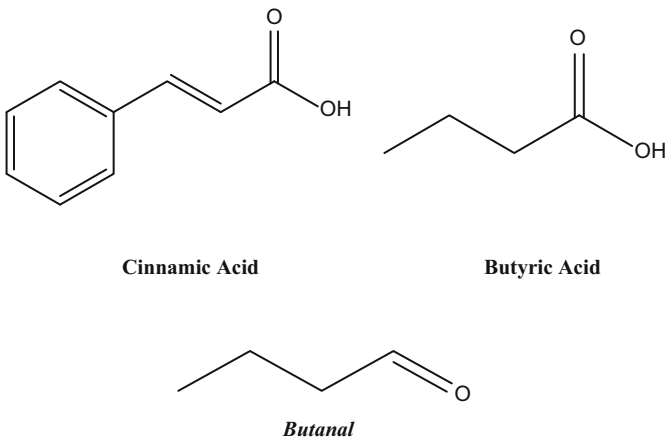
Flavanols and flavones are the two main flavonoids reported from *A. lappa*. Quercetin-3-O-rhamnoside has been reported from the leaves of the plant. Later in the year 1971 Saleh and colleagues reported more phenolic compounds such as luteolin, quercetin, quercetin and rutin from the roots, leaves, fruits, and seeds of *A. lappa* in their work (Saleh and Bohm 1971).

10.3 Volatile Compounds

Until most recently, almost 100 volatile compounds have been reported from *A. lappa.* Details about these compounds (name, species, part, and the analytical techniques employed for isolation and identification) are described in Table 10.2**.** Some of the chemical structures of volatile compounds have also been given Fig. 10.4.

Table 10.2 Some of the volatile compounds reported in *A. lappa*

S. No	Compound name	Formula	Species	Plant origin/part	Analytical method	References
Hydrocarbons						
1	Aplotaxene	$C_{17}H_{28}$	*A. lappa*	Roots	GCMS	Washino et al. (1986)
2	Clovene	$C_{15}H_{24}$	*A. lappa*	Roots	GCMS	Washino et al. (1986)
3	Docosane	$C_{22}H_{46}$	*A. lappa*	Leaves	GCMS	Aboutabl et al. (2013)
4	Eicosane	$C_{20}H_{42}$	*A. lappa*	Roots Seeds Leaves	GCMS	Aboutabl et al. (2013)
5	Hexacosane	$C_{26}H_{54}$	*A. lappa*	Roots Leaves	GCMS	Aboutabl et al. (2013)
Aldehydes						
1	Benzaldehyde	C_7H_6O	*A. lappa*	Roots	GCMS	Washino et al. (1986)
2	Butanal	C_4H_8O	*A. lappa*	Roots	GCMS	Washino et al. (1986)
3	Decanal	$C_{10}H_{20}O$	*A. lappa*	Roots	GCMS	Washino et al. (1986)
4	Heptanal	$C_7H_{14}O$	*A. lappa*	Roots	GCMS	Washino et al. (1986)
5	Octanal	$C_8H_{16}O$	*A. lappa*	Roots	GCMS	Washino et al. (1986)



Cinnamic Acid **Butyric Acid**

Butanal

Fig. 10.4 Some nonvolatile compounds reported from *A. lappa*

10.3.1 Hydrocarbons

Washino and colleagues in their studies on the plant isolated 14 hydrocarbon compounds from the seeds, leaves, and roots of the plant. These include tetradecane, tetracosane, pentadecane, pentacosane, 1-pentadecene, 2-nepthalenemethanol, nonadecane, hexacosane, heptacosane, 1-heptadecene, eicosane, dihydroaplotaxene, cloven, and aplotaxene (Washino et al. 1986).

10.3.2 Aldehydes

Work performed by Wang as well as Washino and colleagues in the year 1986 and 2004, respectively, reported 19 aldehydes namely 4-methoxybenzaldehyde, tridecanal, propanal, pentanal, phenylacetaldehyde, (E)-2-octanal, nonanal, 3-methylpropanal, (E)-2-hexenal, (Z)-3-hexenal, hexanal, heptanal, dodecanal, decanal, butanal, benzaldehyde, octanal, and undecanal from the roots of the plant (Washino et al. 1986; Wang et al. 2005). In literature, there is only one reported aldehyde, alkyl aldehyde nonanal that has been found in all parts of plant, viz. leaves, roots, and seeds (Tables 10.3 and 10.4).

Table 10.3 Some phenolic and flavonoids present in *A. lappa*

Phenolic compounds			Flavonoids		
Compound	R_{time}	ppm	Compound	R_{time}	ppm
Gallic acid	7.627	1.67	Narengin	12.287	142.12
Pyrogallol	7.725	218.35	Hisperidin	12.420	4063.70
4-Aminobenzioc acid	8.793	2.17	Rutin	12.507	633.74
Cataehein	9.220	93.76	Quercetrin	13.373	89.77
Chlorogenic	9.628	124.64	Apeginin-7-glucose	13.600	55.07
Catechol	9.929	59.82	Naringenin	–	
Caffeine	10.248	20.35	Querceitin	14.554	51.73
Vallinic	10.841	9.06	Hispirtin	14.721	72.83
P-hydroxy-benzoic acid	10.393	93.41	Kampferol		
P-coumaric	11.820	24.35	Rhamentin	15.433	54.69
Ferulic	12.013	15.48	Apegnin	154.633	25.95
Iso-ferulic	12.353	4.07			
Alpha-coumaric	13.200	7.83			
Ellagic	13.300	46.20			
Benzoic	13.417	256.99			
3,4,5-methoxy-cinnamic acid	13.953	55.92			

R_{Time} *retention time, ppm* parts per million

Table 10.4 Major nutritional ingredients present in the *A. lappa* (roots)

Types	Nutrient ingredients
Amino acids	Aspartic acid (25–28%) Arginine (18–20%)
Metal elements	Potassium, calcium, iron, magnesium, Sodium, zinc, copper
Vitamins	B1, B2, C, A
Others	Crude fiber, phosphorus, carotene

10.4 Pharmcological Profile of *A. lappa*

In traditional system of medicine *A. lappa* has been extensively used as an ethnomedicinal plant mostly in Europe, Asia, and North America and has been commonly used to treat numerous illnesses like rheumatoid arthritis, gout, Type 1 and 2 diabetes, and dermatological complications (Azizov et al. 2012). The plant has been used for the treatment of various diseases ranging from acute and chronic inflammation, arthritis, and various skin-related problems, namely, rough skin conditions such as eczema and psoriasis to cancer treatments as well (Kolacz et al. 2014b). Its roots have been employed as an antidote to mercury poisoning (Maghsoumi-Norouzabad et al. 2016). *A. lappa* has also been used to treat alopecia (loss of hair) among adults (Kolacz et al. 2014a, b). *It* has shown wide range of pharmacological activities like, anticancer, antidiabetic, antioxidative, anti-inflammatory, antimicrobial, hepatoprotective, gastroprotective, antifertility, antiallergic, and anti ulcerative colitis, etc. Table 10.5 shows the individual compounds possessing biological activity with possible mechanism of actions.

10.4.1 Anticancer Potential

Cancer therapy is very difficult because it is a complex and curatively challenging disease owing to its intra- and inter-tumor heterogeneity, which makes it difficult to target. Since anticancer therapy resistance is increasing day by day, research is being carried out to overcome this resistance. An important approach in this regard is the interdisciplinary approach, wherein research is being carried out to isolate and characterize new bioactive molecules from natural products having significant medical outcome and minimum off-target effects. Bioactive molecules that have been reported from the plant have significant anticancer activities in different cancer cell lines and cancer models.

Arctigenin, a natural lignan, that has been isolated from the seeds of *A. lappa* possesses antitumor activity. Its effect is shown by modulating the tumor cells that are susceptible to the effects of the nutrient-poor environment (Awale et al. 2006). In lung adenocarcinoma, arctigenin is found to increases the proportion of cells in the cell cycle (G0/G1) phase in A549 cell line (Susanti et al. 2013). It also decreases levels of proteins that are involved in GI/S phase checkpoint signaling, including

Table 10.5 General compounds and their effects of burdock (*A. lappa*)

Classification	Compound	Molecular formula	Part of the plant	Reported activity	Reference
Lignans	Arctigenin	$C_{12}H_{24}O_7$	Leaves, fruits, roots, and seeds	• Suppressor of heart shock • Antitumor • Anti-influenza virus	Chan et al. (2010)
	Arctin	$C_{27}H_{34}O_{11}$	Leaves, fruits, roots	• Antitumor promoting activity • Chemo-preventive activity • Antiproliferative activity against B cell hybridoma cell, MH60	
	Trachelogenin	$C_{21}H_{24}O_7$	Fruits	• Ca^{2+} antagonist activity • Anti-HIV properties	
	Lappoal F	$C_{40}H_{42}O_{12}$	Fruits, seeds	• Inhibiting NO production	
	Diarctigenin	$C_{40}H_{42}O_{12}$	Fruits, roots, seeds	• Inhibiting NO production	
Terpenoids	Beta-eudesmol	$C_{15}H_{26}O$	Fruits	• Antibacterial • Antiangiogenic	
Polyphenols	Caffeic acid	$C_9H_8O_4$	Stems, leaves, skin of roots	• Antioxidative. • Free radical scavenging activity	
	Chlorogenic acid	$C_{16}H_{18}O_9$	Leaves, skin of roots	• Neuroprotective. • Antioxidative • Antianaphylaxis • Anti-HIV	
	Tannin	$C_{76}H_{52}O_{46}$	Roots	• Antitumor • Immunomodulator • Hyaluronidase inhibition	
Fructose	Inulin	$(C_6H_{10}O_{5)n}$	Roots	• Prebiotic effectiveness • Antihypertensive • Antidiabetic	

cyclin-dependent kinases CDK2, CDK7, cyclin E & H, nuclear protein mapped to the AT locus (NPAT), and protein cyclin-dependent kinases (p-CDK) (Susanti et al. 2013). In Canadian population, *A. lappa* has been shown to improve health-related quality of life (HRQOL) and check cancer development, and is one the active ingredients present in herbal products, viz. "*Flor-Essence*" and "*Essiac*"

recommended for prolonging of survival and enhancement of health-related quality of life (HRQOL) among cancer patients (Tamayo et al. 2000).

10.4.2 Inhibition of JAK-STAT Signaling

In a study conducted on mice-bearing gain- or loss-of-function gene mutations which encode Janus kinases signal transducer and activator of transcription proteins (JAK-STAT) signaling pathway, it was observed that this pathway emerged as a central means of communication node for the immune system. Work performed by Yao et al. (2011) revealed that arctigenin from *A. lappa* inhibited IL-6 and exerted inhibitory effects on STAT3 tyrosine phosphorylation through suppression of JAK1 & 2 and Schmidt-Ruppin A-2 (Src), a proto-oncogene tyrosine-protein kinase.

10.4.3 Antidiabetic Activity

In traditional system of medicine, roots of *A. lappa* have been used as first choice treatment for diabetes. A study conducted by Ahangarpour and colleagues reported that ethanolic extract of burdock roots administered orally to streptozocin-induced diabetic rats lowered levels of glucose and increased levels of insulin in blood significantly (Ahangarpour et al. 2017). *A. lappa* markedly decreased very low-density lipoproteins (VLDL), serum total cholesterol (TC), and triglycerides (TG) in diabetic mice (Ahangarpour et al. 2017).

10.4.4 Antimicrobial Activity

Roots and leaves of *A. lappa* are eaten in salad in folk medicine. In vitro studies have shown potential prebiotic effect (Moro et al. 2018). Lyophilized leaf extract of the plant exhibited antimicrobial activity, especially against bacteria that are related to endodontic pathogens such *as pseudomonas aeruginosa*, *lactobacillus acidophilus*, *candida albicans*, *and bacillus subtilis* (Pereira et al. 2005). Chlorogenic acid obtained from its root extract has shown antibacterial activity against *Klebsiella pneumoniae* and has also been found to possess anti-β-lactamase activity (Rajasekharan et al. 2017). Besides it also inhibits the formation of biofilm by *Escherichia coli* and *candida* (Chan et al. 2011).

10.4.5 Ulcerative Colitis

T cells (T helper 1 & 17 cells) and other related cytokines are said to be involved in the pathogenesis of ulcerative colitis. *A. lappa* has been shown to give relief against ulcerative colitis. Arctigenin from *A. lappa* inhibited proliferation of T cells in a dose-dependent manner that was induced by concanavalin A. It actually

downregulates RORγt (Wu et al. 2015). There is enough evidence that *A. lappa*, more particularly arctigenin, significantly reduces subarachnoid hemorrhage–induced vasospasm in animal models (Tabassum et al. 2018).

10.4.6 Dermatological Effects of *A. lappa*

People from North America, Asia, and Europe have been using leaves of *A. lappa* and related species for various kinds of dermatological conditions, viz. psoriasis, abscesses, acne, ichthyosis, eczema, boils, and rashes. These actions might be due to the occurrence of phenolic compounds in the plant. Chan and colleagues reported that the antioxidant and anti-inflammatory potential of these compounds assist in detoxifying and mediate healing action of the plant (Chan et al. 2011). Burdock is used as an ingredient in various commercial cosmetic products because of the presence of various hydroxycinnamic acid derivatives which contribute in antimicrobial, anti-inflammatory, anti-collagenase, and anti-tyrosinase activities as well protection against ultraviolet radiations (Ahangarpour et al. 2017).

10.4.7 Hepatoprotective and Gastroprotective Activity

In vivo and in vitro antioxidant potential of the plant has been reported by Duh, Lin, and their colleagues in their work, which also showed that the plant possesses excellent hepatoprotective activity (Duh 1998; Lin et al. 2000). In 2018, Fierascu et al. (2018) reported antioxidant potential of *A. lappa* using phosphomolybdate and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assays and reported that entire extract of burdock exhibits very high antioxidant potential because of the presence of very large quantity of polyphenols. *A. lappa* is also found to possess gastroprotective activity due to presence of 1,3-dicaffeoylquinic acid that has been isolated and characterized from the ethanolic fraction of the plant (Carlotto et al. 2015).

10.4.8 Clinical Trials

In a cohort study conducted in Japan in 2013 on safety and toxicity effects of "GBS-01," an orally administered drug containing arctigenin as one of the ingredient on gemcitabine-resistant pancreatic cancer, patients were given GBS-1. Blood toxicity, dose-limited toxicities, and non-blood of grade 3–4 toxicities were taken as main endpoints after first 4 weeks of the trial. Increase in gamma-glutamyl transferase (GGT), total serum levels of glucose, and bilirubin were some of the adverse effects noted on the oral administration of GBS-01 (Tabassum et al. 2018).

10.5 Conclusion

A. lappa (burdock) seeds, leaves, roots, and fruits contain many phytoconstituents including volatile and nonvolatile compounds that have therapeutic potential against various kinds of diseases. Though roots are more frequently used, other parts of the plant have also shown a good amount of phytoconstituents, and hence promise. A survey into the literature shows that burdock and its isolated compounds possess a wide range of therapeutic uses, viz. anti-inflammatory, anticancer, antidiabetic, anti-obesity, hepatoprotective, and gastroprotective. The promising medicinal uses of the plant, however, necessitate to have an understanding about its adverse effects, while using it for various ailments. Therefore, further studies are important for better understanding of the role of the plant in preventing and treating any disease as well as any associated off-target effects of the plant.

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Marrubium vulgare L.: Traditional Uses, Phytochemistry, and Pharmacological Profile

11

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Abstract

Marrubium vulgare L. (family: Lamiaceae), also known as the white horehound, is a plant with high bioactive potential, thrives almost in any soil, and is naturalized in North and South America and Western Asia as far as India. *M. vulgare*, a traditional herb, belongs to genus *Marrubium*. This plant is widely used as an herbal remedy for chronic coughs and colds. It is used in various disorders related to skin, liver, gastric, heart, and immune system. The main aim of this chapter is to provide the comprehensive information about the traditional uses, pharmacological actions, phytochemistry, and medicinal uses of *M. vulgare* and provides scientific proof for various ethnobotanical claims to identify gaps, which will give impulsion for novel research on *M. vulgare*-based herbal medicines.

Keywords

Marrubium vulgare · Lamiaceae · White horehound · Diterpenoids · Pharmacological properties · Phytochemistry

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11.1 Introduction

Marrubium vulgare L. (*M. vulgare*) has become a worldwide species that originally emerged in the region between the Mediterranean Sea and Central Asia and presently inhabits all continents (KNOSS 2013). *Marrubium vulgar* belonging to the family Lamiaceae is commonly known as "pahari gandana" or "white horehound" and has been used since ancient times for the treatment of various disorders. It grows almost in any soil and is evolved in Western Asia and Northern and Southern America as far as India. It is cultivated at elevations of 5000–8000 ft in Kashmir (Vinayaka et al. n.d.). The name Marrubium is derived from the Hebrew word "*marrob*" which means "*bitter juice*" and *vulgare* means "*well known*" or "*common*." The name "horehound" emerges from the previous words of English "*har*" and "*hune*," which means feathery plant. In the Serbian language, the traditional name is "*ocajnica*" which means a "desperate lady," because tea from this herb was taken by ladies who were not able to conceive (Aćimović et al. 2020).

M. vulgare is a huge, robust, perennial or annual herb, 40–120 cm in height, with branched taproot or various lateral fibrous roots, robust stems, bluntly quadrangular, more rounded below, densely covered with a thick white cottony felt, especially when young (Vinayaka et al. n.d.). The leaves are roundish, ovate, generally toothed, veined, petiolate with the densely wrinkled surface covered with downy hairs, and are sequenced in contrary pairs on a large stem. In the axils of upper leaves, the inflorescence is found, with white flowers in dense axillary whorls. The calyx is tubular, lobed, and 10-toothed, with a minute hooked spine or bristle in each tooth. Corolla is pale to white lavender, bilabiate, and tubular; the upper lip is bilobed, erect, and bifid; while the lower lip is three-lobed with middle lobe is broader. The corolla tube has style, stamens, and anthers with diverse sacs (Yabrir 2019). Pollen grains are radially symmetrical and oblate spheroidal in shape. Flowering occurs in early spring and nectar-gathering bees regularly visit these flowers (Ahvazi et al. 2018). The seeds are found at the bottom of the calyx (Lodhi et al. 2017). The surface of *M. vulgare* is thickly covered with non-glandular and glandular trichomes. Glandular trichomes are of two types: capitate and peltate. Most of the capitates trichomes are long and comprise of the unicellular head with a long stalk neck cell. There are two types of short capitates trichomes too: Those with a bicellular head and those with a unicellular stalk. Peltate trichomes are made up of large heads and short stalk cells with secretory cells sequenced in the form of a loop. The materials secreted by secretory cells cross through apical walls and get assembled in a void between the cell wall layer and the cuticle. The non-glandular trichomes can be multicellular branched or multicellular uniseriate (Dmitruk and Haratym 2014).

Knowing its huge ability for use as a medicine, as well as the constant exploration of its other useful activities, there has been an increasing demand for the growth of *M. vulgare.* The cultivation of this plant is carried out under specific agroecological conditions to supply the raw material with standard quality containing huge content of marrubiin and other diterpenes in addition to phenolics. *M. vulgare* is propagated most often by seeds, through the production of seedlings or direct sowing. The

germination rate is low, that is, 35%, after the collection of mature seeds. However, when stored for 1 month after collection, germination increases to 78–80% (اموازی et al. 2018). Seeds that are sown in fall germinate in the spring, while those that are sown in spring germinate after 21 days. The cropping of *M. vulgare* was greatly influenced by the seed sowing technique. From the cultivation done in the spring, much amount of higher yield was collected from fresh herb than from the one done in autumn (Zawiślak 2009). *M. vulgare* grows well in alkaline soils (Aćimović et al. 2020). Amri et al. (2017a, b) reported that treatment of plant with copper stimulated the activities of antioxidant enzymes particularly superoxide dismutase (SOD) and catalase (CAT) enzymes and increased the total flavonoid (phenolic) content. Based on these results, the authors hypothesized that *M. vulgare* has an innate ability to cope with the stress of Cu by triggering enzymatic and nonenzymatic antioxidant processes.

Boron has a crucial function in cell wall sugar synthesis, nucleic acids, hormones, phenolics, digestion of carbohydrates and proteins, cell elongation, and development of pollen tubes in plants. The extent of toxicity and deficiency of boron, however, is close enough when it is applied to plants that require only a minute amount of boron for essential functions. Ardiç et al. (2018) used a method for the determination of boron content in the specimens (root, stem leaf, and flower) of *M. vulgare* plant known as the curcumin method. Besides that, samples of soil were observed by means of the atomic absorption spectrophotometer technique for boron content. It was confirmed that samples of *M. vulgare* stored boron levels that were three times greater in the stem, more than four times greater in leaves, four times greater in flowers, and approximately three times greater in the root, as compared to the boron concentrations in soil, which revealed that *M. vulgare* can withstand high boron stress.

11.2 Historical Background of *M. vulgare*

There are about 49 accepted species of the genus *Marrubium* (Lamiaceae). Few of the species of *Marrubium* such as *M. vulgare* is used traditionally as a medicinal plant in most of the parts of Europe, Pakistan, Tunisia, France, Brazil, and Morocco (Christiane Meyre-Silva and Cechinel-Filho 2010). *M. vulgare* L. (Lamiaceae) commonly referred to as "*pahari gandana*" or "*white horehound*" has been used from the earliest times as a remedy for various illnesses. Since ancient Egyptian times, it has been used as an expectorant to relieve cough (Blumenthal et al. 2000). In India, it is used to treat acute or chronic bronchitis and whooping cough as an Ayurvedic remedy (Khaled-Khodja et al. 2014). The name "Horehound" is derived from the word "hoary" because of the presence of white hairs that surround horehound leaves and "hound" as it was used to treat bites from rabid dogs in ancient Greek medicine (Khaled-Khodja et al. 2014). In 1927, scholars researched that white horehound can be used in pulmonary diseases (Lodhi et al. 2017). In 1941, it was reported that *M. vulgare* is the most favored pectoral herbal remedy and is used as an expectorant, bitter tonic, and diuretic (Wren 1941). The use of *M. vulgare* as a

decoction of honey syrup to treat bronchitis and coughs was explained in Belgian literature, *Materia Medica Vegetabilis*, in 1954 (Steinmetz 1954). In 1998, *The Physician's Desk Reference for Herbal Medicines* proposed the common uses of white horehound for pulmonary catarrh, acute as well as chronic bronchitis, respiratory infections, tuberculosis, asthma, jaundice, and externally for damage of skin and ulcers. Because of the presence of bitter ingredients particularly marrubinic acid as a choleretic agent, juice, and infusion of *M. vulgare* is used internally as a gastric secretion stimulant. In Germany, *M. vulgare* is traditionally used as a bitter tonic where as in Anglo-American and Mediterranean, it is used for respiratory diseases (KNOSS 2013). Paste of leaves is rubbed on boils and also applied for rheumatism. Infusion of dried herb is taken in weakness and in case of high blood pressure. Infusion of leaves, flowers, and stem are used as a stomachic, for cardiac problems and diabetes (Quattrocchi 2012).

White horehounds are commonly used in Norfolk and some other areas of England to cook tea, sweets, and ale. It was used by the Romans and Egyptians as an antidote to poisons. When sprayed on fruiting plants, an infusion of White Horehound helps to kill cankerworms. It was believed that digestion was eased, intestinal worms were killed, and heartburn was relieved. People used to chop nine small leaves and mix them with a tablespoon of honey at the first symptom of a cold and then chew gently to relieve a sore throat (Barrett 2009). In Brazil, white horehound has been traditionally used to combat inflammation, gastrointestinal diseases, and respiratory disorders (Meyre-Silva et al. 2005). The juice of green herb or decoction of dried herb and seeds of *M. vulgare* is taken along with honey, which is a treatment for short-winded cough. To cure wounds of dog bites, an ointment prepared from boiled green leaves was used (Culpeper 2006). An infusion of leaves is used against caterpillars and as an insecticide (Dar et al. 2020).

11.3 Medical Importance of *M. vulgare*

In terms of ethnomedicine, the Lamiaceae is the most diverse plant family. It has great medicinal value because of the presence of volatile constituents in it (Sarac and Ugur 2007). As an infusion, it is given as a stimulant, anthelmintic, and resolvent in the doses of one to two fluid ounces. It is also used for dyspepsia, amenorrhea, hepatitis, and chronic rheumatism (Haq et al. 2011; Singh and Panda 2005). *M. vulgare* is also used as a flavoring agent in beverages and candies in the USA (Lodhi et al. 2017). The volatile oil present in *M. vulgare* has prominence in common people for normalizing irregular heartbeats because of the presence of marrubiin. The hot white horehound infusion creates a sweat-inducing effect, and the cold infusion is used for the digestive system as a bitter tonic. *M. vulgare* has also been used to cure malaria and to suppress fevers (Mabey et al. 1988). The tea of *M. vulgare* herb is taken as a suppressant for cough and expulsion of catarrh. Directions were given by *Materia Medica Vegetabilis* for the composition of decoction of *M. vulgare* in conjunction with honey to treat bronchitis and cough (Van Tellingen 2007). In current phytotherapy, several herbal medicinal products

from *M. vulgare* are given in cough associated with cold as an expectorant and as the characteristic therapy for temporary lack of appetite and for minor dyspeptic symptoms such as bloating flatulence (Aćimović et al. 2020; Thomas and Thomas 1920). It has been revealed that the traditional use of *M. vulgare* involves the therapy for dysmenorrhea, jaundice, and in higher doses as laxatives in addition to their use in the treatment of respiratory diseases (Akther et al. 2013; Kanyonga et al. 2011). Also, it is used externally for damages to skin, wounds, and ulcers (Amri et al. (2017a, b)).

Novel approaches related to pharmacological importance of *M. vulgare* has revealed that it has several in vivo and in vitro activities such as antioxidant, antidiabetic, antihypertensive, anti-inflammatory, digestive stimulant, effect on respiratory system, hypolipidemic, anti-asthmatic, antifungal, and antibacterial activities (Meyre-Silva and Cechinel-Filho 2010). Extensive phytochemical studies on *M. vulgare* revealed that there are about 54 secondary metabolites present in it. Some of these metabolites involve sesquiterpenes, diterpenes, flavonoids, and phenylpropanoids, and were spotted in various parts of *M. vulgare* (Knoss 1994; Nawwar et al. 1989; Sahpaz et al. 2002a). The major diterpenes present in *M. vulgare* are marrubiin, marrubinic acid, and marrubenol which possess anti-edematogenic and analgesic activities. Phenylpropanoids such as acteoside, arenarioside, ballotetroside, and forsythoside B exhibit potential anti-inflammatory and anticancer activities. Chemically, marrubiin, a furane labdane diterpene, is the main component of this plant and possesses potent antinociceptive properties and vasorelaxant activity (Yabrir 2019; اهوازی et al. 2018). The extracts of *M. vulgare* and its metabolites have been found to have the potential for treating cardiovascular diseases and type II diabetes (Ardiç et al. 2018). The antidiabetic potential of *M. vulgare* has been attributed to marrubiin, a furanoid diterpene lactone that represents the main metabolite of *M. vulgare* (Amessis-Ouchemoukh et al. 2014; Mittal and Nanda 2016; Verma et al. 2012).

11.4 Taxonomy

BINOMIAL NAME *M. vulgare*

The genus *Marrubium* belongs to the Lamiaceae family. The Lamiaceae Martinov (=Labiatae Adans., the mint family) has a global distribution with more than 7200 species among approximately 240 genera (Bräuchler et al. 2010). In the plant list database (http://www.theplantlist.org), there are near about 120 scientific names of the plant species for the genus *Marrubium*, but out of these only 49 are accepted species names. The genus is dispersed in temperate regions of Europe, North Africa, and Asia to western China with a few species inhabited in North and South America (Ahvazi et al. 2016). Many species of the Lamiaceae family are given more importance, particularly *M. vulgare* because of its uses in food, cosmetics, and medicine (Khaled-Khodja et al. 2014). Horehound is the most well-known common name for this genus and white horehound is the English name for *M. vulgare* in all of the global areas in the world (Spiteri 2011; اهوازی et al. 2018). The name Horehound

Table 11.1 Taxonomic hierarchy of *Marrubium vulgare* plant

Taxonomic hierarchy	
Rank	Scientific name and common name
Kingdom	Plantae—plants
Subkingdom	Viridiplantae—green plants
Infrakingdom	Streptophyta—land plants
Superdivision	Embryophyta—seed plants
Division	Tracheophyta—vascular plants
Subdivision	Spermatophytina—spermatophytes, phanerogames
Class	Magnoliopsida
Superorder	Asteranae
Order	Lamiales
Family	Lamiaceae—mints, menthes
Genus	*Marrubium* L.—horehound
Species	*Marrubium vulgare* L.—white horehound, horehound

comes from the two words, the word "hoary," due to the white hairs present on the surface of hoar leaves and "hound," because it was used in the earliest times as Greek medicine to treat bites from rabid dogs (Blumenthal et al. 2000) (see Table 11.1).

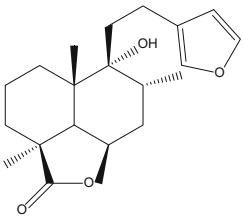
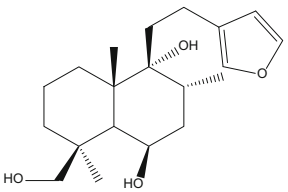
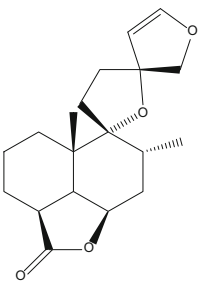
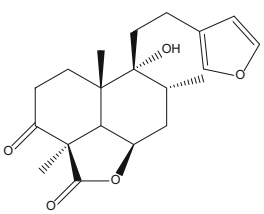
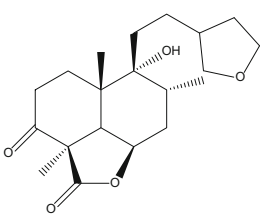
11.5 Phytochemistry of *M. vulgare*

The Marrubium herb (aboveground parts) is collected just before acquiring green color. *M. vulgare* has a bitter taste and sweet odor that turns into an acrid odor by drying (Lodhi et al. 2017). Earlier phytochemical studies have revealed the occurrence of lactones, alkaloids, flavonoids, steroids, phenylpropanoid esters, tannins, vitamin C, and diterpenoids in *M. vulgare* (Masoodi et al. 2015; Christiane Meyre-Silva and Cechinel-Filho 2010). More than 54 secondary metabolites from various parts of white horehound have been extracted and identified. The major groups of constituents, some of which demonstrate possible pharmacological activities in vitro and in vivo, are known to include diterpenes, sesquiterpenes, and flavonoids (see Table 11.2).

11.5.1 Diterpenoids

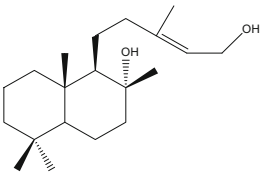
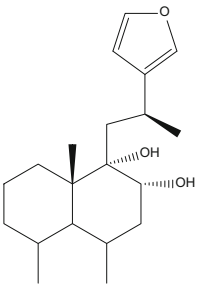
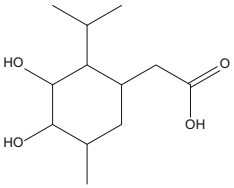
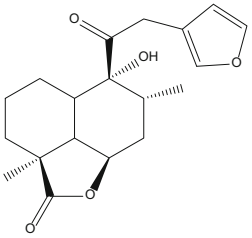
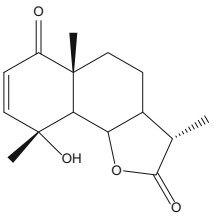
Diterpenoids constitute the large group of constituents present in aerial parts of *M. vulgare* (Piozzi et al. 2006). There are nine distinct kinds of diterpenes along with their alcoholic derivatives which have been recognized and isolated from *M. vulgare* (Rodrigues et al. 1998). Marrubiin is a diterpenoid unsaturated γ-lactone, extracted from aerial parts of *M. vulgare* (Busby et al. 1983). Few diterpene alcohols such as marrubiol, peregrinin, marrubenol, dihydroperegrinin, and sclareol have also been extracted from flower tops and leaves of *M. vulgare* (Kowalewski and Matlawska

Table 11.2 Structures of active constituents of *M. vulgare*

Active constituent	Structure	Reference
Marrubiin		Verma et al. (2012)
Marrubenol		Amessis-Ouchemoukh et al. (2014)
Premarrubiin		Amessis-Ouchemoukh et al. (2014)
Peregrinin		Masoodi et al. (2015)
Dihydroperegrinin		Masoodi et al. (2015)

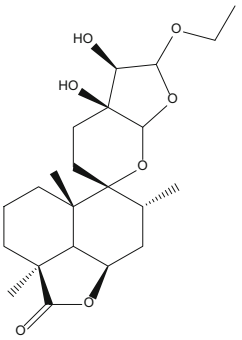
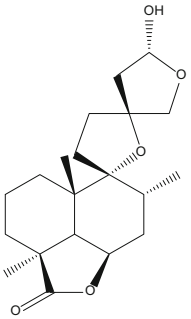
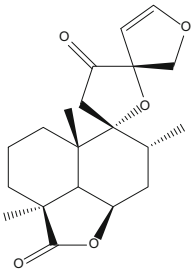
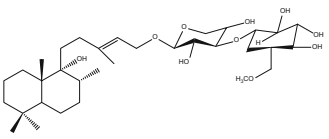
(continued)

Table 11.2 (continued)

Active constituent	Structure	Reference
Vulgarol		Verma et al. (2012)
12(S)-hydroxymarrubiin		Masoodi et al. (2015)
Marrubic acid		Ahmed et al. (2010)
11-Oxomarrubiin		Shaheen et al. (2014)
Vulgarin		Verma et al. (2012)

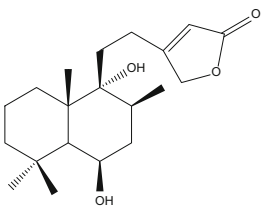
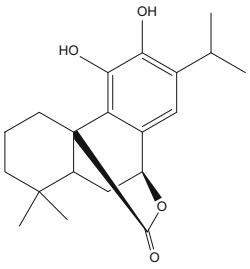
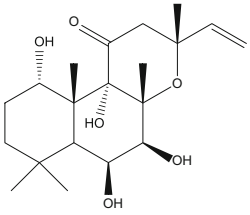
(continued)

Table 11.2 (continued)

Active constituent	Structure	Reference
Marruliba-acetal		Amessis-Ouchemoukh et al. (2014)
Cyllenin A		Piozzi et al. (2006)
Polyodonine		Shaheen et al. (2014)
Vulgarcoside A		Shaheen et al. (2014)

(continued)

Table 11.2 (continued)

Active constituent	Structure	Reference
Deacetylvitexilactone		Amri et al. (2017a, b)
Carnosol		Paunovic et al. (2016)
Deacetylforskolin		Amessis-Ouchemoukh et al. (2014)

1978; Popa et al. 1968; Puri and Hall 1998). Premarrubiin, premarrubenol, marruliba-acetal, cyllenil A, polyodonine, preleosibirin, peregrinol, vulgarol, vulgarcoside A, deacetylforskolin, carnosol, deacetylvitexilactone have also been identified in the shoots of *M. vulgare* (Henderson and McCrindle 1969; Knoss 1994; Popa and Pasechnik 1975). The study revealed that the labdane skeleton is the precursor for the synthesis of several diterpenes and in the biogenesis of marrubiin which in plantlets and shoot culture of *M. vulgare*, follows a non-mevalonate pathway (Knöss et al. 1997). The presence of furanic labdane diterpene has also been reported in distinct parts of *M. vulgare* (Knöss and Zapp 1998). 11-Oxomarrubiin, which is a new secondary metabolite, was reported from *M. vulgare* methanolic extract of the whole plant (Shaheen et al. 2014). Two novel labdane diterpenoids, 3-deoxo-15-methoxyvelutine and 12(*S*)-hydroxy-marrubiin were reported from *M. vulgare* methanolic extract of the whole plant collected from Srinagar, Kashmir, India (Masoodi et al. 2015).

11.5.2 Essential Oils Including Monoterpenes and Sesquiterpenes

Saleh and Glombitza (1989) claimed essential oils like β-pinene, bisabolol, β-elemone, isomenthon-8-thiol, and tricyclene as the principal constituents of *M. vulgare*. Other constituents of essential oil that were investigated are isocaryophyllene, γ-cadinene, and β-bisabolene (Weel et al. 1999). In Egypt, Salama et al. (2012) claimed that γ-cadinene and thymol as the principal components of *M. vulgare* oil. From Libya, El-Hawary et al. (2013) claimed that the major constituents of *M. vulgare* volatile oil were thymol, (E)-β-farnesene, and carvacrol. In Tunisian, Hamdaoui et al. (2013) stated that β-caryophyllene (7.8%), (E)-β-farnesene (7.4%), and β-bisabolene (28.3%) are the major constituents that contain *M. vulgare* essential oil. Abadi, Hassani, and Algeria (Abadi and Hassani 2013a) suggested that the main constituents of the oil of *M. vulgare* were *δ*-cadinene (3.13%), germacrene D-4-ol (9.61%), benzaldehyde (2.31%), 4,8,12,16-tetramethyl heptadecan-4-olid (16.97%), phytol (4.87%), dehydrosabinaketone (4.12%), piperitone (3.27%), α-pinene (9.37%), and 1-Octen-3-ol (2.35%). In Iran, approximately 44 compounds were identified in the essential oil from aerial parts of *M. vulgare* by gas chromatography–mass spectrometry (GC-MS) (Lodhi et al. 2017). The principal constituents were as (E)-β-farnesene (11.39%), α-pinene (6.64%), β-caryophyllene (32.19%), and 1,8-cineole (8.17%).

Approximately 20% of sesquiterpenoids were identified and reported in the flowering tops of *M. vulgare* (Nagy and Svajdlenka 1998). In Iran, the aerial (aboveground) parts of *M. vulgare* were found to contain essential oils and about 47 distinct components were isolated and analyzed by gas chromatography–mass spectrometry. The main components were β-caryophyllene, (Z)-β-farnesene, germacrene D, and α-humulene (Khanavi et al. 2005; Morteza-Semnani et al. 2008). A new monoterpene, from the whole plant of *M. vulgare*, has been identified as p-menthane-5,6-dihydroxy-3-carboxylic acid also named marrubic acid (Ahmed et al. 2010). Another study reported that 34 constituents were found in the oil, constituting 95.1% of the overall oil. The essential oil was identified to contain a large number of sesquiterpenes (82.5%) with β-caryophyllene (11.6%), β-bisabolene (25.4%), and (E)-β-farnesene (8.3%) as the main constituents. Vulgarin, a sesquiterpene lactone, has been extracted from *M. vulgare* aerial parts. Few other terpenes reported in essential oil of leaves and flower tops of *M. vulgare* are limonene, p-cymol, alpha terpinolene, sabinene, para fenchene, and sabinene.

11.5.3 Flavonoids and Their Glycosides

Flavonoids are an essential class of compounds and are commonly distributed in several plants. More than 10 flavonoid constituents, glycone, as well as aglycone glycosides are recorded from various sections of *M. vulgare*. A total of 11 flavonoids, including some glycosides, were extracted from the leaves of *M. vulgare* such as vitexin, quercetin, chrysoeriol, isoquercetin, luteolin, apigenin, apigenin 7-O-glucoside, luteolin 7-lactate, luteolin 7-O-beta-D-glucoside, quercetin 3-O-alpha-1-

rhamnosyl-glucoside, apigenin 7-(6″-p-coumaroyl)-glucoside (Atta-ur-Rahman 2013; Nawwar et al. 1989). Flavone-derivative 3-hydroxyapigenin-4′-O-(6″-O-para coumaroyl)-beta-D-glucopyranoside has been isolated from *M. vulgare* whole plant methanolic extract (Shaheen et al. 2014). Ladanein was first isolated from the extract of dichloromethane of the aerial parts of plant *M. vulgare* (Alkhatib et al. 2010). 7-O-beta-glucuronyl luteolin was first identified from *M. vulgare* along with other compounds such as 5,6-dihydroxyflavone (ladanein) and 7-O-beta-glucopyranosyl luteolin (Pukalskas et al. 2012).

11.5.4 Phenylpropanoid and Phenylethanoid Glycosides

Few phenylpropanoids, for example, (+) (E)-caffeoyl-L-malic acid, ballotetroside, acteoside, forsythoside B, and arenarioside were isolated from flowering tops of *M. vulgare* in 2002 (Popa and Pasechnik 1975; Sahpaz et al. 2002a). Verbascoside and forsythoside B have been isolated with a solvent combination of methanol–water–acetic acid (79:20:1) from aerial sections of *M. vulgare* (Pukalskas et al. 2012). Vulgarcoside A, diglycoside diterpene, has also been isolated from methanol extract of the whole plant of *M. vulgare* (Shaheen et al. 2014). Few new phenylethanoid glycosides, such as marruboside and acetyl marruboside, have been isolated from aerial sections of *M. vulgare* (Sahpaz et al. 2002b).

11.5.5 Miscellaneous Compounds

Two phytosterols, two phenolic acids, and traces of alkaloids from *M. vulgare* were identified in addition to the above compounds. From the aerial portion of *M. vulgare*, a pentacyclic triterpene called ursolic acid, and steroids like stigmasterol and β-sitosterol, plus two phenolic acids, gallic acid, and caffeic acid were recorded (Laonigro 1979; Nawwar et al. 1989). Trace quantities of pyrrolidine betonicine alkaloid and its isomer turicine were obtained from the leaves and flower tops (Daniel 2006; Hoffmann 2003). In 2010, few usual alkanes and four forms of branched alkanes, that is, 2-(omega-1)-dimethylalkanes, 2-methylalkanes, 3-methylalkanes, and 3-(omega-9)-dimethylalkanes, were extracted from *M. vulgare* aerial parts (Christiane Meyre-Silva and Cechinel-Filho 2010).

Mittal and Nanda (2016) revealed that Marrubii herb has a total ash content of 10.70%, total fiber content of 9.50%, a water-soluble ash content of 8.90%, and an insoluble ash content of 1.73%. Mittal also stated that the value of alcohol soluble extractive was 8.66%, indicating that most of the plant ingredients were soluble in alcohol. In comparison, the value of hydrosoluble extractive is roughly 5.90%, while the value of petroleum ether soluble extractive is 2.77% (see Table 11.3).

Table 11.3 Quantitative estimation of physicochemical parameters of *Marrubium vulgare* (Mittal and Nanda 2016)

S. no.	Parameters	Mean	S.D.
01	Moisture content (w/w)	17.2	±0.35
02			
03	Total ash (w/w)	10.7	±0.46
04	Acid-insoluble ash (w/w)	1.73	±0.61
05	Water-soluble ash (w/w)	8.9	±0.65
06	Alcohol-soluble extractive (w/w)	8.66	±1.2
07	Water-soluble extractive (w/w)	5.90	±0.8
08	Petroleum ether-soluble extractive (w/w)	2.77	±0.3
09	Total fibre content (%)	9.5	±0.88

11.6 Pharmacological Properties of *M. vulgare*

Some prominent pharmacological properties associated with *M. vulgare* are as follows:

11.6.1 Hepatoprotective Property

The hepatoprotective properties of the whole plant methanol extract were tested for hepatotoxicity caused by paracetamol. In albino Wistar rats, hepatotoxicity was caused by the administration of paracetamol (2 g /kg), p.o. for 7 days. *M. vulgare* methanol extract was administered at doses of 100 and 200 mg/kg/day, p.o. for 7 days. To measure the levels of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, gross bilirubin, and triglycerides, serum analysis was carried out. The estimation of glutathione and malondialdehyde was done on the liver after it was isolated and homogenized. Histopathology studies were also conducted on the catalase liver samples (Akther et al. 2013).

11.6.1.1 Effect of MEMV on Marker Enzyme in Serum

It was found that the chronic oral administration of paracetamol (PCM) caused serious liver damage which was indicated by a remarkable spike in the marker enzymes ALT, AST, ALP, and triglyceride level ($P < 0.01$) relative to that of the control group. Significant protection against PCM toxicity was seen in the animals that were treated with methanolic extract of *Marsdenia volubilis* (MEMV—100 and 200 mg/kg along with PCM by restoring the levels of ALT, AST, ALP in dose-dependent manner. After the PCM insult, a remarkable increase in overall bilirubin was found ($P < 0.01$). As was observed with serum triglyceride levels ($P < 0.01$), the effect of MEMV on total bilirubin was dose dependent.

11.6.1.2 Effect of MEMV on Albumin

Albumin levels in the class treated with PCM alone were greatly reduced. Remarkable ($P < 0.01$) and dose-dependent elevations in protein concentration in liver tissue were caused by MEMV therapy at both doses. The group treated with silymarin also reported a substantial increase in albumin levels in comparison to the group treated with PCM alone. MEMV's reversal of elevated serum enzymes in PCM-mediated liver damage may be due to membrane stabilization, thus avoiding intracellular enzyme leakage. This is in line with the generally accepted belief that serum transaminase levels return to normal with hepatic parenchyma healing and hepatocyte regeneration (Vadivu et al. 2008).

For biochemical analysis, histopathological findings have also provided supporting evidence. MEMV therapy has changed cellular morphology substantially in a dose-dependent manner. These findings demonstrate that MEMV's hepatoprotective action may be due to the presence of antioxidants (phenolic type (87%) or flavonoid type), that is, marrubiin, marrubinol, and monoterpene, such as marrubic acid present in *M. vulgare* (Kadri et al. 2011), which have shown antioxidant activity. The impact of 200 mg/kg MEMV was greater than 100 mg/kg and was equal to the standard as demonstrated by the percent protection showing increased cellular stability and metabolic activity. In the extract-treated classes, the toxic effects of paracetamol were greatly controlled, which was manifested by the restoration of serum biochemical parameters to a near-normal level. It has been concluded that *M. vulgare* has major hepatoprotective properties.

The whole plant aqueous extract of *M. vulgare* was examined for antihepatotoxic activity against hepatic damage caused by CCl_4 in male Wistar rats. This extract in a dose of 500 mg/kg body weight for 7 days was compared with the standard drug silymarin 10 mg/kg body weight. This extract lowered the raised levels of serum enzymes such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), and increasing total proteins (TP) and possessed remarkably antihepatotoxic activity (Masoodi et al. 2015).

Examination of the antihepatotoxicity and therapeutic effect of 7:3 v/v ethanol/water extract and petroleum ether extract on the toxicity of liver cell caused by CCl_4 in mice manifested that parameters of kidney and liver function persisted at adequate levels in groups reacted with *M. vulgare* extract. The superoxide dismutase (SOD) and catalase (CAT) activity was significantly increased by the administration of *M. vulgare* ethanolic extracts. And also the total antioxidant capacity was increased with a decrease in the concentration of lipid peroxide when extracts were used as therapeutic or protective agents (Ibrahim et al. 2014). The histopathological examination of liver damage caused by CCl_4 in rats and measurement of parameters of lipid profile such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), reduced glutathione (GSH), superoxide dismutase (SOD), and malondialdehyde (MDA) were used to evaluate the antihepatotoxic activity of 80:20 v/v ethanol/water extracts of *M. vulgare* in the varying concentrations of 100, 200, 300, and 400 mg/kg. By lowering the levels of AST and ALT significantly, different extract concentrations showed considerable

antihepatotoxic effect but there was a small decrease in the levels of ALP. As far as the antioxidant activity is concerned, these extracts showed a remarkable decrease in SOD and contents of GSH and MDA. These studies manifested that various concentrations of *M. vulgare* shield the liver against hepatotoxicity caused by CCl_4 and the benefit can be due to its antioxidant activity (El-Hallous et al. 2018).

11.6.2 Antioxidant Activity

Oxidative stress is caused by the disproportion in the process of homeostasis between antioxidants and oxidants in the body as a result of free radicals. The main cause of aging and the number of human ailments like diabetes, cancers, neurodegenerative disorders rheumatoid arthritis, etc. is believed to be because of oxidative stress (Halliwell 1999). The substances that retard, avert, or cease the oxidative damage to target molecules are called antioxidants (Mbah et al. 2019). Butylated hydroxyl anisole (BHA) and butylated hydroxyl toluene (BHT) are very effective but have a dark side as they may trigger tumors at high doses after long-term treatment. To replace synthetic antioxidants used in food, cosmetic, and pharmaceutical products, there is an increased interest in naturally occurring antioxidants. Free radical scavenging assay and 2,2-diphenyl-1-picrylhydrazyl (DPPH) have been used to find the in vitro antioxidant properties of *M. vulgare* methanol extracts and the results suggested an adequate antioxidant activity (Yousefi et al. 2016). By using the same method to determine the antioxidant activity, it was found that essential oil of *M. vulgare* displays IC_{50} value of 153.84 μg/ml which is around twice the value higher than a synthetic antioxidant butylated hydroxyl toluene (BHT) (Abadi and Hassani 2013b). The strong antioxidant activity of methanolic and acetone extracts of *M. vulgare* was ascertained by photo chemiluminescence (PLC) assay which evaluates the compound's antioxidant activity in the presence of superoxide anion radicals, reactive oxygen species (ROS) produced in the human body also but lower activity was detected on the examination of essential oil and isolated marrubiin (Rezgui et al. 2020).

11.6.3 Antiproliferative Activity

Traditionally *M. vulgare* is frequently used in the treatment of cancer (Bourhia et al. 2019), but the basic mode of action and clinical legitimacy of its application continue to be discovered. *M. vulgare* methanolic extract was assessed using a luminescence method for its proliferative effect in vitro, it was stated to be the most potent (Okur et al. 2019). It has been found (Zarai et al. 2011) that *M. vulgare* essential oil can prevent the proliferation in cervical cancer (HeLa) cell line with an IC50 value of 0.258 μg/mL. The ethanol/water extracts (70:30) of *M. vulgare*, in a dose-dependent manner, decreased the feasibility of melanoma (B16) and glioma (U251). The findings revealed that this plant may be a successful candidate for anti-melanoma and anti-glioma therapy by displaying the capacity of extracts of *M. vulgare* to

hinder multiplication of cells, cytoprotective autophagy, and induce apoptosis (Paunovic et al. 2016). Acacetin, alcoholic extracts, apigenin, and acacetin-7-rhamnoside demonstrated a strong degree of anticancer activity against breast carcinoma, while anticancer activity against Ehrlich tumor cell lines was found in all compounds examined. Another research (Alkhatib et al. 2010) demonstrated the moderate effect of labdanein (methoxylated flavone) from *M. vulgare* on human myeloid leukemia (K562) and human B cell precursor leukemia cell lines (697), as well as on imatinib-resistant human myeloid leukemia (K562R) cells. These findings provide a typical basis for the potential ladanein-derived flavones to be hemi synthesized in future and the study of their antileukemic activity.

11.6.4 Anti-inflammatory Activity

In a rat model, studies related to the anti-inflammatory activity of *M. vulgare* methanolic extracts on isoproterenol-induced myocardial infarction found that 52.2–69.0% of serum creatinine kinase-MB was subsidized (depending on the dosage of *M. vulgare* extract). Furthermore, therapy with extracts greatly decreased the activity of myocardial myeloperoxidase in myocardial infarction (Yousefi et al. 2014). In the serum of rats with myocardial infarction, levels of tumor necrosis factor-alpha (TNF-alpha) have decreased dramatically. Moreover, all doses of the extract greatly decreased the peripheral neutrophil count. Besides, 3-hydroxyapigenin-4 J-O-(6JJ-O-p-coumaroyl)-β-D-glucopyranoside, 11-oxomarrubiin, and vulgaroside A from the *M. vulgare* methanol extract demonstrated medium to low levels of NO synthesis inhibition, whereas vulgaroside A also exhibited average inhibitory effects on pro-inflammatory cytokinine TNF-α (Shaheen et al. 2014). *M. vulgare* glycosidic phenylpropanoid esters have been demonstrated to inhibit the cyclooxygenase (COX) enzyme activity, which plays an important role in the conversion of arachidonic acid to pro-inflammatory prostaglandins and is associated with inflammation (Sahpaz et al. 2002a).

The evaluation of anti-inflammatory function has shown that that orally administered 200 mg/kg of methanolic extract of *M. vulgare* to carrageenan-treated rats lowered the rate of inflammation (87.30%) relative to diclofenac (standard positive control) (Ghedadba et al. 2016). The study reveals that marrubiin from *M. vulgare* used in a model of microvascular leakage in mice ears demonstrates important and dose-related anti-edematogenic effects. Marrubiin therapy triggered a dose-dependent inhibition of extravasation of Evans blue in mice ears caused by carrageenan, bradykinin, and histamine, with maximum inhibitions of 63.0%, 70.0%, and 73.7%, respectively. Moreover, the ovalbumin-induced allergic edema was substantially blocked by marrubiin in actively sensitized animals. These findings indicate that a nonspecific inhibitory effect is applied through the systemic administration of marrubiin (Stulzer et al. 2006). The assessment of anti-inflammatory activities against carrageenan and prostaglandin E2-induced inflammation and analgesic activity on the p-benzoquinone-induced abdominal

constriction test indicated that *M. vulgare* methanolic extract has an activity close to that of indomethacin and acetylsalicylic acid as reference drugs (Kanyonga et al. 2011).

11.6.5 Antidiabetic Activity

As an antidiabetic agent, *M. vulgare* has an ethnomedical record (Hamza et al. 2019). Several attempts have been made to collect clinical evidence supporting its conventional application in the regulation of diabetes mellitus (Rodríguez Villanueva et al. 2017). It was shown by Chakir et al. (2015) that the oral ingestion of *M. vulgare* methanolic extract to diabetic rodents (diabetes induced with streptozocin), caused a substantial decrease in the number of glucose levels of blood, uric acid, creatinine, and serum urea as well as rectification of lipid profiles. Such methanolic extracts have greatly improved skeletal muscles and liver glucose absorption. Contradictory to this, the absorption of glucose of the inverted rat jejunum was decreased. Such findings indicate that the impact of *M. vulgare* extract can be attributed to extrapancreatic processes. This antidiabetic activity is the result of the regulation of glycogen synthesis and the blockade of absorption of intestinal glucose. Alkofahi et al. (2017) tested 21 plants grown in Jordan on Sprague–Dawley rats at 1 g/kg for their antihyperglycemic activity where a neutral influence on blood glucose levels was demonstrated by *M. vulgare* extract.

Another study (Elmhdwi et al. 2015) shows the activity of various *M. vulgare* extracts (water, methanol, and butanol) on cyclosporine and streptozotocin-mediated autoimmune diabetes mellitus. A drop in interferon-gamma (IFN-γ), NO levels of pancreas, and blood glucose levels was shown by the class of animals treated with *M. vulgare* extracts in contrast to the diabetic mice. A substantial reduction in overall cholesterol, low-density lipoproteins (LDL) cholesterol, very-low-density lipoproteins (VLDL) cholesterol, and triglycerides have also been induced by *M. vulgare* extract. After the therapy of *M. vulgare*, the serum insulin levels as well were dramatically increased.

11.6.6 Antimicrobial Activity

Essential oil of *M. vulgare* has a prominent impact on microorganisms, particularly Gram-positive bacteria having MIC values and inhibition zones in the range of 1120–2600 μg/mL and 6.6–25.2 mm respectively, while Gram-negative bacteria have greater tolerance. *Botrytis cinerea* demonstrated the powerful reaction to the essential oil of *M. vulgare* with a zone of inhibition of 12.6 mm, when its antifungal effect is observed. But *Aspergillus niger*, *Fusarium solani*, and *Penicillium digitatum* were little susceptible to this essential oil (Zarai et al. 2011). One research was performed to detect the antifungal effect of flavonoids (flavanols and flavans) derived from *M. vulgare* leaves against two fungal strains: *Candid albicans* ATCC 10231 and *Aspergillus niger* ATCC 16,404. The MIC detected ranged between 6.25

and 100 μg/mL and resulted in extreme antifungal inhibition, which also surpassed the already advertised activity of antifungals (amphotericin, terbinafine, econazole nitrate, and fluconazole) due to which *M. vulgare* flavonoids were marked as potentially potent antifungal agents (Bouterfas et al. 2016). It was also summarized by Rezgui et al. that *M. vulgare* can be used for the treatment of skin dermatophyte infections as antifungal agents (Rezgui et al. 2020).

11.6.7 Antihypertensive Activity

The aqueous extract of *M. vulgare* is commonly used as the therapy for hypertension in the earliest times traditionally. Marrubenol, marrubiin, and furanic labdane diterpenes were discovered as the most active compounds by bioactivity-guided fractionations, chemical derivatization, and spectroscopic examination (El Bardai et al. 2003). Through the study of the effects of 10-week therapy with amlodipine and *M. vulgare* water extract on the systolic blood pressure, cardiovascular remodeling, and vascular relaxation in automatic hypertensive rats, it was found that treatment with *M. vulgare* resulted in a decrease in systolic blood pressure. Moreover, it had an important antihypertrophic effect in the aorta and strengthened relaxation of a mesenteric artery caused by acetylcholine (ACh) (El Bardai et al. 2004).

11.6.8 Wound-Healing (Hemostatic) Activity

Studies of the use of *M. vulgare* methanolic extract in wound repair have shown that the extract rich in marrubiin (6.62%) and polyphenolic compounds such as flavonoids and other phenylethanoid glycosides has wound-healing and antioxidant properties by facilitating fibrosis proliferation and cell migration (Amri et al. 2017a, b). The evaluation of hemostatic behavior by the process of plasma recalcification indicated the unexpected dose-dependent anticoagulant action of *M. vulgare* aqueous extract (Ghedadba et al. 2016).

11.6.9 As a Natural Pesticide

An extract derived from plant *M. vulgare* was checked against mosquito *Culex pipiens*' fourth larvae of instar. The obtained results suggested the sensitivity of *Culex pipiens*' larvae. The sensitivity was increased when larvae exposure time to insecticide was prolonged. With 900 mg/mL and a 72-h exposure to the extract of *M. vulgare*, the greatest mortality rate (94%) was attained, while a 59% mortality rate was attained with 900 mg/mL and a 72-h exposure time. These findings could provide a chance to use some easily available, inexpensive plants that are mostly harmless to various living organisms to develop alternatives to environmentally hazardous chemicals (Amel and Sélima 2015). The *M. vulgare* volatile oil is

remarkably toxic to both *Schistosoma mansoni* and *S. haematobium* species of snails (Saleh and Glombitza 1989). In Spain, *M. vulgare* is being commonly used to avoid lice and frequent scratching of animals on chicken farms, which has increased its cultivation on farms (Rezgui et al. 2017). Moreover, the seed germination and seedling growth of *Sinapis arvensis* and *Lactuca sativa* under laboratory conditions was remarkably affected by *M. vulgare* extract of leaves and extract of rhizosphere soil. Although the allelopathic effect relies on target species, these extracts can be used to manage weeds in crop fields as an effective source of natural herbicides (Dallali et al. 2017).

11.7 Toxicity

In vivo experiments in rats found no acute toxicity from *M. vulgare* dry extract (2000 mg/kg) obtained from methanol maceration (1.5 kg air part/4 L). No skin or eye and nasal mucosa modifications have been observed (Paula de Oliveira et al. 2011). A single dose of dry extract (1 g/kg body weight, prepared with 1 g of dried herb/50 mL of purified water) was given orally to mice in another in vivo assay (Paula de Oliveira et al. 2011). Without an apparent change in weight or behavior, the animals were observed for 7 days. After 1 h of intake, only mild tachycardia was detected. No anatomical or histological modifications indicating poisonous or mutagenic effects were discovered after the eighth day (Jaouhari et al. 1999).

11.8 Conclusion

In the current chapter we have made an effort to survey and contribute the utmost information of historical background, geographical distribution, traditional claims, and phytochemical and pharmacological information of *M. vulgare*, a remedial herb employed in the school of medicine. Study of literature displayed the presence of diterpenoids, essential oils, flavonoids, phenylpropanoid, and phenylethanoid glycosides in various parts of plant were discovered. *M. vulgare* exhibited hepatoprotective activity along with other important activities such as anti-inflammatory, antioxidant, antiproliferative, antihypertensive, wound healing, and other activities. This chapter will undoubtedly come to the aid for the researchers and practitioners, handling with this plant, to know its nature and properties. Due to its indispensable value, it is not incorrect to portray that this plant is magnificent conventional plant.

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Cichorium intybus: A Comprehensive Review on Its Pharmacological Activity and Phytochemistry

12

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Abstract

Cichorium intybus, commonly called chicory, is a biennial herb belonging to family Asteraceae. The plant is considered to originate 4000 years ago in Europe and grows in Asia, America, and Africa. Italy is known to cultivate chicory on large scale for the production of seeds. Ayurvedic system of medicine considers the plant as an essential medicinal herb. Various systems of medicine like Unani, Siddha, and Ayurveda utilize the medicinal herb as remedy for anorexia, disorders of renal system, and dyspepsia. Leaves are considered to contain high levels of total phenolic and total flavonoid content as compared to other parts of chicory plant. Roots possess near about 40% inulin. Chicory is considered to possess numerous active phytochemicals like vitamins, flavonoids, sesquiterpenes, chicoric acid, chicorin and caffeic acid, etc. that are responsible for its bioactivity. Due to the presence of such active phytoconstituents, it has been traditionally used in folklore medication in numerous parts of the world. The plant is reported to be the best substituent for coffee. Ancient Egyptians have cultivated chicory as medicinal plant and since decades it had been used

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medicinally in regions where the plant has been adopted as well as in indigenous regions. Reported literature on the plant evidences a number of pharmacological activities including antidiabetic, anti-inflammatory, hepatoprotective, antimalarial, etc. Besides these pharmacological activities, it has been found to be highly potent against gram-positive bacteria, fungi, and helminths. The basic rationale of the chapter is to provide a comprehensive review of various therapeutic activities of the plant and phytochemical moieties responsible for medicinal repute of *C. intybus*.

Keywords

Chicorin · Bioactivity · Medicinal repute · Chicory · Sesquiterpenes

12.1 Introduction

Cichorium intybus, a biennial herb, belonging to family "Asteraceae" is commonly known as chicory. It is called as "Kasani" in Sanskrit (Zafar and Ali 1998). The plant's name has been obtained from Latin as well as from Greek, *Cichorium* corresponds to "domain" whereas, *intybus* means "to crack" (in Greek) and *tubus* indicating "empty stem" (in Latin). The two different names for *intybus* are attributed to the leaves (Ema 2010). The plant is considered to be one of the most essential medicinal plant in the Ayurvedic system of medicine (Rizvi et al. 2014). It is a herbal plant consisting of 14 species. It is extensively grown in temperate parts of the world and mainly in the Mediterranean region, northern Asia, and north Africa. The plant is indigenous to Europe (Sastri 1962). In indigenous medicines, plants of the genus *Cichorium* (Asteraceae) are used abundantly (DerMarderosian and Beutler 2002). In Unani, Siddha, and Ayurvedic systems of medicine, this medicinal plant is used to treat renal system disorders, hepatobiliary system, dyspepsia, and anorexia (Tyler et al. 1988; Crellin and Philpott 1990). The plant possesses rosette leaves and tuberous taproot and is usually upright and glandular (Zafar and Ali 1998). It is a tiny biennial aromatic herb, possessing blue or white flowers (Nandagopal and Kumari 2007). The plant tolerates a vast range of climatic and soil conditions, is considered a cosmopolitan weed (Simon et al. 1996).

The most popular reference sources like *Physicians Desk Guide for Herbal Medicines* and German Commission e-monographs reported that the *C. intybus*, due to the existence of sesquiterpene lactones, cinnamic acid derivatives, and flavonoids, can be used for negative chronotropic and inotropic effects and against loss of appetite (Fleming 2000). Chicory extract has been rated as "generally considered safe" by the Food and Drug Administration (FDA) and described in "Everything Added to Food in the United States" (Schmidt et al. 2007). The existence of vitamins, such as ascorbic acid (Gilani and Janbaz 1994), thiamine, riboflavin, retinol, carotenoids and niacin (Wills et al. 1986), inulin, sesquiterpenes, that is, esculin, esculetin, cichorin A, lactucin, zinc, hydroxycinnamic acid, and lactucopicrin was discovered in comprehensive phytochemical work on the plant

material (Vg and Dranik 1972). Caffeic acid, cichoric acid as a quinic acid monoester, and isorhamnetin as a variety of flavonoids are contained in the leaves of plant. Cichoriolide A; cichorioside A, B, and C; along with some other known sesquiterpenes are contained in roots of the plant (Bais and Ravishankar 2001). The bitter taste of chicory is ascribed to the presence of these sesquiterpene lactones (Peters and van Amerongen 1998). As chicory is a hardy plant, thus during both vegetative and reproductive growth stages it can survive extreme temperatures (Bais et al. 2000). All parts of the plant transude milky latex on breakage (Van Wyk et al. 1997). *C. intybus* is being cultivated for a wide variety of applications, and hence according to the use, plant has been divided into four major varieties or cultivation classes:

1. Root chicory or industrial chicory is mainly confined to northwestern part of Europe, Chile, India, and some regions of South Africa. These regions cultivate conical root which is used as substituent in coffee manufacture and for extraction of inulin.
2. Witloof chicory or Brussels is usually grown within Europe for the production of buds that are etiolated.
3. Aerial (leaf) chicory has been used fresh or sometimes cooked as vegetables.
4. Silage chicory, originally obtained from chicory that's usually wild variety, is more often found by the side of roadways and barren land. This kind of chicory has been used to increase acquisition of herbage in perennial pastures for livestock since the mid-1970s (Cadalen et al. 2010).

However, various plant parts have global utilization pertaining to conventional medicine due to its widespread distribution (Süntar et al. 2012). The basic constituents are contained in the root but some of the important phytochemical constituents have been found to be present throughout the plant (Bais et al. 2000).

12.2 Historical Background and Distribution

C. intybus belonging to Asteraceae family, originated 4000 years ago in Europe, several parts of Asia, America, and Africa. Egyptians used *C. intybus* in medicinal practices and its use in folk medicine is widely recorded. Although the beginning of the cultivation of chicory is not established exactly, but a Roman historian called it "Plinius" and registered it with lettuce about 50 AD (Kiers et al. 1999). In the North of Europe, it was used as fodder until the seventeenth century. The use of chicory for pasture in England was pioneered by Elliott. In New Zealand, chicory was first reported in the year 1867. In Pennsylvania, until 1993, chicory was classified as a noxious weed (Jung et al. 1996). Historically, chicory was cultivated as curative herb, veggies crop, and coffee replacement by the ancient Egyptians and was sometimes used for animal feed. It was discovered in the 1970s that 40% of the inulin was contained in roots of *C. intybus*, that possess marginal effect on plasma glucose and hence considered to be ideal for the treatment of diabetes (Judžentienė

and Būdienė 2008). Up to date, *C. intybus* is grown on an industrial scale for the production of inulin (van Arkel et al. 2012). It is one of the most frequently used herbal regimen and a multipurpose edible plant in east Anatolia known as kanej, tahlisk, or hindiba. Turkey's eastern Anatolia area is very mountainous and highly fractured, so it provides favorable conditions for diverse plant growth (Özgökçe and Özçelik 2004). Wild chicory can be found in coastal areas and in the mountains in Italy. Demands are growing in Italy at the moment and some seed companies have begun to grow wild chicory seeds. It is also well known not only in the different regions of Italy (Guarrera and Savo 2013), but also in India, north and south Europe (Bais et al. 2000), and in Spain (Benítez et al. 2010). For thousands of years, chicory has been a component of natural grasslands in many parts of the world, but as a forage crop, it only has a relatively recent past. This plant is considered to be a nutritious forb that is used in the summer for grazing ruminants to create available forage with high nutritional value (Barry 1998).

12.3 Morphology

Cichorium, a plant species comprising diploid cells ($2n = 18$) belonging to the family of Asteraceae, subfamily of Cichoriodeae, tribe of Lactuceae or Cichorieae (Funk et al. 2005), is generally referred to as witloof chicory. Wild chicory species is perennial, but as a biennial species, the crop has been selected for cultivation (Kiers et al. 1999). *Cichorium* is an upright arboreous plant extended to about 90–100 cm length and possessing 75 cm long fleshy taproot and wide basal leaves (Bais et al. 2000; Van Wyk et al. 1997). This plant also possesses stout tap root that is roughly hairy or glabrous. The length of stem is usually 15–150 cm. In short, the basal leaves are petiolate, oblanceolate, toothed to runcinate. The cauline leaves are found to be sessile. The capitulum usually 2.5–3.5 cm wide is contained in axillary. The outer phyllaries of the plant are ovate whereas inner phyllaries are lanceolate and usually two to three times longer than ovate (Yıldırımlı 1999). The color of the leaves is usually red and the color of flowers varies from bright blue to white or pink. The fleshy root of the plant grows up to 75 cm and fresh buds are often found near the surface of soil. The flowers open at the beginning of the day and close during the afternoon. On the basis of flecked or multicolored leaves or more or less uniformly colored red blades, the Italian red variety of chicory was determined (Roustakhiz and Majnabadi 2017).

12.4 Traditional Uses

All over the world, medicinal plants have been used for millennia, and in order to meet the primary health care needs, various communities still depend on indigenous medicinal plants. In traditional cultures, the informative knowledge of plant-based remedies is likely to progress by trial and error and the most informative knowledge of plant-based remedies and major therapies have precisely moved sequentially

through generations (Gurib-Fakim 2006). Long ago, ancient Egyptians have cultivated chicory as a medicinal plant and since decades it had been used medicinally in the region where the plant has been adopted as well as in the indigenous region (Wang and Cui 2011). The numerous customary or regional names that identify this plant may be attributed to the extensive usage of unique folklore communities. Various preparations of chicory plant are used for the treatment of different ailments (1). It is said that juice acts as a therapeutic to cure uterine cancers and neoplasm (Judžentienė and Būdienė 2008). Leaves and roots have been used to prepare tea as remedy for jaundice in South Africa; although it is considered a common herb, syrup made from the chicory plant is used as tonic and as purifying drug for babies (Van Wyk et al. 1997). Turkey has formulated an ointment from the leaves of chicory for wound healing (Sezik et al. 2001). Whole plant or sometimes only individual plant parts have been used traditionally to prepare decoction of chicory. As per the data in European Monograph, roots of chicory have been traditionally used to solace the indications associated with disorders of digestive system (e.g., distended abdomen, borborygmus, and sluggish assimilation) and reduced appetite (Sile et al. 2020). The flowers (*Cichorii flos*) of this plant are considered to be herbal remedy for regular illnesses like appetite stimulants and analeptic; in addition, these flowers are also used for the treatment of gallstones, bruises and cuts, gastroenteritis, and sinus issues (Judžentienė and Būdienė 2008). The whorls in Italy are turned into a decoction and used as a depurative (Pieroni 2000). Jigrine, an Indian commercial commodity which is used as therapeutic for numerous liver ailment, contains *Cichorium* seeds as one of the key ingredients (Ahmed et al. 2003). Owing to extensive distribution, various plant parts have been possibly used worldwide in conventional medicine, including in Turkey. The roots and leaves are used for diverse purposes in Turkish folk medicine. Chicory roots have been utilized to form decoction that can be consumed against cancer and kidney stones. In other parts of the world, various other health benefits have also been reported. In Afghanistan, aqueous extract of chicory roots had been used against malaria (Bischoff et al. 2004). In Iran this plant was used as therapy for warts (Syed et al. 2008). In Poland, it is used for the treatment of digestive ailment and liver disease (Kisiel and Michalska 2002). In Italy and Serbia, it is consumed as a diuretic and laxative (Pushparaj et al. 2007). In Pakistan, its roots are utilized to form a poultice which is used for the relief of pain (Shah et al. 2006). Similar to Turkey, dried chicory root is also used in Belgium, France, and the USA to prepare coffee-like drinks and as stomachic (Mulinacci et al. 2001). In India, aqueous seed extract is used for the treatment of liver disease and diarrhea (Gadgoli and Mishra 1997), while fresh shoots are eaten as food and used for stomach ache and urinary tract infections (Shah et al. 2006). Biological activity assessment studies have revealed that the complete plant extract of *C. intybus* exhibits antidiabetic and hepatoprotective activity (Pushparaj et al. 2007; Gadgoli and Mishra 1997), whereas highest antioxidant potential, anthelmintic and antimicrobial potential is possessed by the aerial parts of the plant (Foster et al. 2011). On the other hand, various other pharmacological benefits, such as analgesic, antimalarial, anti-inflammatory, anti-ulcerogenic,

and anticarcinogenic activities have been reported for the plant roots (Wesołowska et al. 2006; Conforti et al. 2008).

12.5 Pharmacological Activities

12.5.1 Hepatoprotective Activity

The disorders of liver have been categorized in the high priority regions of healthcare system. As reported by World Health Organization, it has been estimated that approximately 500 million humans are affected by aliments of liver, most often chronic hepatitis (Al-Asmari et al. 2014). Medicines that have originated from plants may also function as practicable remedy for triumphing liver problems due to their safety, less complicated availability, being environment friendly, and for their price effectiveness (Izzo et al. 2016).

As per numerous studies, chicory had a long history of restorative use and especially it is being used as a tonic for ailments of liver and digestive tract (Street et al. 2013). One of the studies reported the decreased levels of serum enzymes (aspartate transaminase and alanine aminotransferase) and bilirubin in carbon tetrachloride (CCl_4) that prompted hepatic damage due to increased levels of serum enzyme and bilirubin; on the other hand, the tiers of albumin and proteins reduced in rats treated with *C. intybus* root callus and natural root extracts. One more study proposes that the ingredients from cultured chicory, cells are greater powerful antihepatotoxic as compared with that of herbal root extract in opposition to carbon tetrachloride (CCl_4)-prompted hepatic harm (Elgengaihi et al. 2016). Furthermore, seeds of chicory are used in biliary disorders together with jaundice and are substances used in several recipes prescribed by means of traditional healers to reduce hepatobiliary proceedings (Said 1982). Yet another study evaluated that the hydro-methanolic extract of *C. intybus* shoots afforded safety against acetaminophen-triggered hepatotoxicity in rats (Gilani et al. 1993). However, a scientific study on the effect of seeds in liver harm is missing. In the same investigation, crude extract of chicory seeds were examined against acetaminophen as well as toward carbon tetrachloride (CCI4), which caused liver injuries, to further authenticate the conventional use of this plant in hepatic harm.

12.5.2 Anti-Inflammatory Activity

Inflammation is defined as protection reaction of body to perilous stimuli along with allergens and/or harm to the tissues; however, out-of-control inflammatory reaction is the main cause of an enormous sequence of problems inclusive of hypersensitive reactions, cardiovascular dysfunctions, metabolic syndrome, most cancers, and autoimmune sicknesses, forcing vast economic burden on individuals and therefore on the society (Bagad et al. 2013). Inflammation and oxidative stress are rigorously interlinked processes that involve the mechanism of releasing numerous nuclear

factor κB (NF-κB)-mediated seasoned inflammatory mediators (Keshk et al. 2017). The process of inflammation involves regulation of extensively merged signals that are mediated through AMP-activated protein kinase (AMPK) and NF-κB. AMPK, a multisubstrate serine or threonine protein kinase, plays regulatory roles in oxidative pressure, irritation, autophagy, mitochondrial dysfunction, and cell destiny (Chen and Zhu 2016).

One of the in vitro research has reported the anti-inflammatory activity of *C. intybus* roots (Cavin et al. 2005).Various models of inflammation have been characterized to evaluate the anti-inflammatory activity of experimental compounds but carrageenan-induced inflammation based on molecular mechanism is widely used. The production of histamine, leukotrienes, and cyclooxygenase merchandise are associated with early phase of carrageenan edema, even as the behind schedule segment for carrageenan-induced response of inflammation is related to infiltration of neutrophils and the release of neutrophil-extracted unfastened molecules, along with superoxide radical, hydrogen peroxide, and hydroxyl radicals, and also to the release of further neutrophil-extracted inflammatory agent (Vinegar et al. 1969). Another research study on *Cichorium* roots concluded full-sized, dose-based decrease in paw edema in carrageenan-triggered paw edema technique. Chicory roots reduced the serum TNF-α, IL-6, and IL-1 stages. They also significantly diminished malonyl aldehyde ranges and elevated the sports of catalase and glutathione peroxidase in paw tissue. Similarly, chicory roots confirmed an extensive lower in granuloma formation in cotton pellet brought about granuloma technique. The roots of *C. intybus* contain anti-inflammatory activity, and this might be because of the inhibition of various cytokines, antioxidants, and their loose radical scavenging pastime (Huang et al. 2012).

12.5.3 Gastroprotective Activity

One of the key issues of contemporary gastroenterology is the treatment of gastroduodenal ulcers (Krylova et al. 2015). Although there are numerous preventive measures and modern therapeutic methods, recurrence occurs in about 30–80% cases despite using highly effective antiulcer regimen. In about 25–40% sufferers, there are chances of complicated peptic ulcers and 14–20% sufferers have been found to be impervious to maximum up-to-date treatment options. Furthermore, traditional regimen motive side effects of numerous types in nearly one-third of patients (Krylova et al. 2015). During the ulcerogenic situation there is domination of aggressive factors even though the protecting factors are reduced. The underlying cause of both the parameters include disorder in metabolism and synthesis of nucleic acids and proteins (Ivashkin et al. 2003). As per the study conducted on dry *C. intybus* root extract (CRE), it has been found to be a favorable approach for the treatment of gastrointestinal illnesses of various etiology. This extract is received through earliest technology, its efficiency is justified on diverse version systems of experimental gastroenterology (Ivashkin et al. 2003). In yet another study, the incidence of ulcer reduced three to nine times after pretreatment with chicory root

extract (25 and 50 mg/kg) within the rat gastric mucosa (Krylova et al. 2015). There has been no change in the volume of gastric secretion by using chicory root extract (CRE) in a dose of 25 mg/kg; at the same time, there was reduction of 44% secretion tension indistinguishable to that in response to famotidine using 50 mg/kg dose of CRE. Same study evaluated remarkable increase of pH values in reaction to both doses, and famotidine indicated a significant decrease of gastric acidity in rats with ulcers and thus it was concluded that CRE has a remarkable inhibitory effect on acid peptic factor (Krylova et al. 2015).

12.5.4 Antidiabetic Activity

Diabetes mellitus is a group of metabolic disorders that outline an elevated level of blood glucose with decreased insulin degrees, and has been regularly associated with insulin resistance, high blood pressure, dyslipidemia, and obesity (Saltiel 2001). Obesity is fundamentally the idea of insulin resistance in type 2 diabetes, that's characterized through insulin resistance and beta-cell disorder of pancreas (Masters et al. 2010). M_1 macrophages and activated M_2 macrophages are the basic two types of adipose tissue macrophages (Fujisaka et al. 2009).When there is an imbalance in the ratio of M_1/M_2 macrophages, there is weight gain that causes obesity and hence there occurs stimulation of M_1 macrophages and downregulation of M_2 macrophages, leading to persistent infection and the propagation of metabolic dysfunction inflicting diabetes (Kraakman et al. 2014). Traditionally, *C. intybus* provides an expansion of fit-to-be-eaten products and is extensively used as an essential medicinal herb to treat diverse ailments, including diabetes (Li et al. 2014). Pharmacologically, the roots of *C. intybus* had been proposed to possess antidiabetic activity (Pushparaj et al. 2007). Evident from various studies type 2 diabetes can be prevented by omega-3 fatty acids through the inhibition of NOD-, LRR-, and pyrin domain–containing protein 3 ($NLRP_3$) inflammasome activation (Yan et al. 2013). Thus, one of the studies on this plant proposed that the plant extract inhibited high-fat diet (HFD)-prompted IL-1b manufacturing via inhibition of HFD-induced $NLRP_3$ inflammasome activation. Also, there is an impairment of insulin receptor signaling due to HFD-induced interleukin (Wen et al. 2011). Thus, this study suggested that chicory remedy might improve the HFD-prompted insulin resistance and hence decreased HFD-brought about IL-1b production. One of the examiner analyzed the effect of *C. intybus* methanolic (CME) extract on glucose delivery and adipocyte differentiation in 3T3-L1 cells by reading the radiolabeled uptake of glucose. The radiolabeled glucose uptake assay was used to evaluate different extracts (hexane, ethyl acetate, and methanol) of *C. intybus*. The maximum glucose uptake was shown by methanolic extract. CME exhibited dose-established growth in glucose uptake and concentration of 100 ng/ml was found to be the ideal dose showing maximum glucose uptake (Nam et al. 2001). Another study investigated the effect of leaves of *C. intybus* in inhibiting protein tyrosine phosphatase 1B (PTP1B), and evaluated the key markers involved in insulin cellular signaling and adipogenesis by utilizing 3 T3-L1 adipocytes (Byon et al. 1998).

Purification studies guided by bioactivity enhanced the additive outcomes of chlorogenic acid.

One more study on the plant proposed that methanolic extract of *C. intybus* contains chlorogenic acid in combination with other caffeic acid derivatives. The 2-deoxy-D-three [H]-glucose uptake was enhanced when methanolic extract and chlorogenic acid was incubated with 3 T3-L1 adipocytes and also there was an inhibition of adipogenesis by altering markers of adipogenesis and signaling of insulin. The in vivo studies have evaluated the effect of CME on insulin sensitivity in diabetic rats. The insulin sensitivity as well as plasma metabolic profile was restored on supplementation of CME for 2 weeks. Same study concluded that the caffeoyl derivatives of leaves of *C. intybus* had promising pharmacological effect on homeostasis (Gum et al. 2003).

12.5.5 Antimicrobial Activity

The antibacterial potential of naturally affluent acid extract of *C. intybus* has been investigated on periodontopathic bacteria consisting of *Prevotella intermedia*, *Streptococcus mutans*, and *A. naeslundii*. Oxalic acid, shikimic acid, quinic acid, and succinic acid are active compounds isolated from *Cichorium* extract. Adhesion of microorganism to the cells and biofilm formation was lowered using these natural acids with one of a kind tiers of efficacy (Gazzani et al. 2000). One of the promising study on *C. intybus* proposed that the crude aqueous and natural seed extracts possess significant antimicrobial activity in opposition to various pathogenic bacteria, specifically, *Candida albicans*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*, and extract of the roots had mentioned outcomes for *B. subtilis*, *Staphylococcus aureus*, *Salmonella typhi*, *Micrococcus luteus*, and *Escherichia coli (*Rub and Sasikumar 2016*)*. Chicory leaf extract has also confirmed a moderate interest in opposition to multidrug resistant *S. typhi* (Rani and Khullar 2004). Root extracts rich in guaianolides have proven antifungal residences against anthropophilic fungi. Phytoalexin cichoralexin, a sesquiterpenoid remoted from this plant, manifested strong antifungal interest in opposition to *Pseudomonas cichorii* (Monde et al. 1990). One of the studies on ethanol, ethyl acetate, and aqueous extract of *C. intybus* has shown significant antibacterial activity, but ethyl acetate extract has notably shown the maximum activity. The growth of *Agrobacterium tumefaciens*, *Erwinia carotovora, Pseudomonas fluorescens*, and *Pseudomonas aeruginosa* was inhibited by aqueous extract. Comparative studies suggest that ethyl acetate extract has the best pastime with respect to all examined bacterial species. *P. aeruginosa* become the maximum sensitive and had the widest zones of inhibition. Root extracts have greater extensive antibacterial activity than extracts from complete plant (Keles et al. 2001). Another research proposes hydroalcoholic and ethanol extracts of chicory (15 mg/mL) showed the significant activity towards *S. aureus*. On the opposite hand antifungal activity was shown by aqueous extract of *C. intybus* whereas ethyl acetate extract lagged antifungal activity (Rehman et al. 2014).

12.5.6 Antioxidant Activity

The foundation motive of the development and continuation of several diseases is oxidative stress. An optimistic way of fighting the undesirable results of reactive oxygen species (ROS) triggered oxidative damage can be diminished using exogenous antioxidants or boosting endogenous antioxidants. The attenuation of ROS due to oxidative harm can be reduced by wide range of nonenzymatic antioxidants synthesized by plants. Antioxidants notably put off oxidation of oxidizable substrates when the substrate concentration is higher than antioxidants (Halliwell 2007). Antioxidants like reduced glutathione (GSH) and superoxide dismutase (SOD) are synthesized in vivo and some are obtained from dietary supplements (Halliwell 2007; Sies 1997). Exogenous antioxidants are mostly obtained from plants. It is reported that among all the plant species existing on earth, majority of plant species have medicinal importance, and first-rate antioxidant capability is shown by almost all the plant species (Krishnaiah et al. 2011). One of the study reported that the extracts of red chicory possess cytoprotective, antioxidant, and antiproliferative sports in Caco-2 intestinal cell fashions. A modulating impact at the oxidative strain caused via 4-tert-octylphenol and hepatotoxicity was shown by extracts of red chicory.

A huge boom within the tiers of thiobarbituric acid reactive materials (TBARS) and bilirubin, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and gamma-glutamyl transpeptidase was observed in rats receiving 4-tert-octylphenol. The *C. intybus* extract modulated the abnormalities on account of the harm due to 4-tert-octylphenol and also caused the reduction in superoxide dismutase, glutathione, and catalase which is an endogenous antioxidant enzyme. Various biochemical and antioxidant parameters were improved and TBARS levels were reduced (Saggu et al. 2014). The antioxidant activity of *C. intybus* was confirmed by extracts rich in polyphenols and morphological modifications in Caco-2 cells was also validated in the extract due to the presence of polyphenols. The above study also confirmed that the 17 μmol/L concentration of polyphenol fraction possessed mild antioxidant activity, whereas cytotoxic consequences, reduced transepithelial electric resistance, elevated permeability, and altered epithelium were confirmed at concentrations of 70 μmol/L and 34 μmol/L respectively. Oxidative strain and cellular harm was reduced by the extracts of *C. intybus* and also in vitro Caco-2 cellular version was triggered (Azzini et al. 2016).

According to a study conducted by (Lante et al. 2011), the red chicory extract was found to contain highest anthocyanin content, that is, 313.1 μg/g (31.31 mg/g of sample). Another study was conducted by (Sahan et al. 2017), and they proposed *C. intybus* contained free phenolic compounds. There was a marked distinction inside the phenolic compound content material as the sample used for the study of antioxidant activity produced significant effervescence. For the optimized crimson chicory extract, the EC_{50} value was determined in correlation with anthocyanin concentration. From the remaining percent of DPPH as a feature of the attention ratio of the anthocyanins, the EC_{50} value was calculated and promising results were

obtained and thus radical scavenging capacity was found to be associated with a decrease EC_{50} fee (Brand-Williams et al. 1995).

One more study for antioxidant evaluation was conducted on *C. intybus* juices using the centrifugation of the plant via micellar model device linoleic acid/b-carotene and hence it was concluded that it has antioxidant activity. The pro-oxidant components had been thermally instable because the boiled juice has shown promising antioxidant activity. Juice additives from *C. intybus* have been fractionated with the aid of sequential dialysis. The presence of numerous antioxidant compounds having different molecular weight and polar features have been noticeably evaluated from *C. intybus* by reversed-phase high-performance liquid chromatography (RP-HPLC) technique. The fraction of *C. intybus* extract that contributes to antioxidant activity is retained by molecular weight 300,000 Da dialysis membrane (Papetti et al. 2002). In yet another study the polyphenols-wealthy fraction of *C. intybus* was subjected to DPPH radical scavenging activity (Heimler et al. 2009). Polyphenol content and evaluation of antioxidant activity of this plant was determined by means of artificial 2,2-diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl radical by the reaction catalyzed with the aid of relevant enzymatic assets for reactive oxygen species, particularly, diaphorase, xanthine oxidase, and myeloperoxidase. Evaluation of antioxidant activity was done by synthetic radical and the enzyme-catalyzed reactions and thus total phenolics were extensively correlated with antioxidant activity (Lavelli 2008). Another research proposed dose-dependent inhibition of xanthine oxidase enzyme using hydroalcoholic extract of aerial parts of *C. intybus* (Pieroni et al. 2002). Additionally, chelated ferrous ion and inhibited hydrogen peroxide were observed for DPPH radical scavenging activity of *C. intybus (*Nehir El and Karakaya 2004*)*.

12.5.7 Antimalarial Activity

The antimalarial use of *C. intybus* has been reported on the basis of its traditional use in Afghanistan as the fresh roots of plant have been reported to be used as regime for malarial fevers. Isolated bitter compounds namely lactucopicrin, lactucin, and guaianolide sesquiterpenes from aqueous extract of *C. intybus* have been reported to possess significant antimalarial activity. One of the studies conducted on plasmodium falciparum reports inhibition of the HB3 a dead ringer for strain Honduras-1 of *Plasmodium falciparum* using 10 μg/mL and 50 μg/mL concentration of lactucin and lactucopicrin respectively (Bischoff et al. 2004). The Walter Reed Army Medical Research Institute validated the inhibitory action of lactucin (complete inhibition at 10 μg/mL) and lactucopicrin (complete inhibition at 50 μg/mL) as the parallel outcomes were observed for a light unprotected crude ether extract of chicory root. One more study proposes the use of ether extract of chicory against W-2 strain of *Plasmodium falciparum* and D-6 strain (clone of Africa). The ether extract has been observed to be moderately energetic in opposition to the W-2 strain of *Plasmodium falciparum* (Indochina clone, IC50 = 243.4) and weakly energetic against the D-6 strain (clone of Africa). These mixed consequences supply credence to the Afghan

claim of a light-sensitive plant treatment for malaria. Different structurally associated sesquiterpene lactones and isolated compounds like lactucin and lactucopicrin are likely additives of an aqueous extract and hence presence of such compounds in fresh aqueous extract might show various degrees of antimalarial activity and that the collective activity may also provide an cheaper, quite simply available alternative or adjunct remedy to the affliction (Kisiel and Zielińska 2001).

12.5.8 Anthelmintic Activity

One of the most generic and economically vital pathogens in cattle across the world are nematode parasites of the gastrointestinal tract, particularly in animals which can be grazed outside (Fitzpatrick 2013). For the evaluation of anthelmintic potential of subsidiary metabolites found in chicory plant, various studies are conducted. Thus, several studies reported that grazing of animals on *C. intybus* had better overall performance based index, also the incidence of nematode in gastrointestinal tract decreased. Enormous studies on the plant have shown promising results of anthelmintic activity due to the presence of condensed tannins and sesquiterpene lactones (Miller et al. 2011).

Anthelmintic activity of this plant has been additionally observed for lambs. The study proposed that the lambs consuming this plant had lesser number of abomasal helminths (Marley et al. 2003). Larval migration inhibition assay has been used to evaluate the efficacy of sesquiterpene-rich extract and condensed tannins in opposition to deer lungworm larvae, *Dictyocaulus viviparus* and some larvae of gastrointestinal nematode. Another study investigated on both lungworm and gastrointestinal nematodes, *C. intybus* was found to produce a dose-dependent decrease in larval motility (Molan et al. 2003). Egg hatching of *Haemonchus contortus* was also inhibited using sesquiterpene lactone-rich extracts of *C. intybus*. Significant reduction in survival of third-stage larvae of *Ascaris suum* has been reported using purified *C. intybus* extract (Williams et al. 2014).

12.5.9 Analgesic Activity

Analgesic activity of *C. intybus* was evaluated using hot plate and tail-flick test. In both the tests analgesic movement in mice was exhibited using lactucopicrin, 11β, 13-dihydrolactucin, and lactucin. In the recent study, all three compounds exerted an analgesic effect was exerted by all the three compounds, but the compound lactucopicrin produced maximum effect. Evaluation using tail-flick test, 30 mg/kg dose of the tested compounds produced antinociception effect akin to 60 mg/kg dose of ibuprofen. As glaring from the reduced spontaneous locomotor activity in mice compounds like lactucopicrin and lactucin were also reported to possess sedative action (Wesołowska et al. 2006).

12.5.10 Tumor Inhibitory Activity

C. intybus has been evaluated for tumor inhibitory activity. One of the studies proposed that ethanolic crude extract of roots of chicory produced widespread hampering of Ehrlich neoplasm in mice. Also, 70% growth inside lifestyle stretch become discovered using intraperitoneal dose of tested extract equal to 500 mg/kg/day (Hazra et al. 2002). Antiproliferative impact on amelanotic melanoma C32 mobile strains was exerted by aqueous alcoholic macerate of *C. intybus* leaves (Conforti et al. 2008). Compounds like Magnolialide, 1β-hydroxyeudesmanolide remoted from chicory roots constraint various tumor mobile traces and differentiation of human leukemia U-937 and HL-60 cells to cells resembling monocytes and macrophages was also prompted (Lee et al. 2000).

12.5.11 Antiparasitic Activity

Gastrointestinal (GI) parasites are responsible for causing infections in grazing farm animals worldwide, along with scientific and subclinical sicknesses due to which agricultural economies and food manufacturing could be markedly impaired (Fitzpatrick 2013). In 1980s, *C. intybus* was selected for feeding farm animals and thus the first industrial forage variety (Grasslands Puna) was released. Henceforth, there has been the development of various forage *C. intybus* cultivars (Rumball et al. 2003). Authentic evidence of *C. intybus* as an antiparasitic has been furnished through novel research involving in vitro assays and excessive outturn chemical profiling of the tested extracts of the plant. As described by Foster et al., sesquiterpene lactone–rich extracts from two forage *C. intybus* cultivars ("Grasslands Puna" and "Forage Feast") have been reported to bring about a dose-dependent inhibition of egg hatching in unfastened-living degrees of *H. contortus*. One of the researches identified the main guaianolide of *C. intybus* in the tested extracts and reported multiplied ovicidal pastime of the Grasslands Puna extract (Foster et al. 2011). Recent studies have proven that the *C. intybus* extract containing sesquiterpene lactone have effective and dose-dependent in vitro pastime against parasitic levels of livestock nematodes (grown up *Cooperia oncophora* and *Ostertagia ostertagi*), that are predicted to be important targets of nutritional supplements in the host (Pena-Espinoza et al. 2015).

12.5.12 Renal Impairment

A wholesome kidney is vital for glucose homeostasis. The glucose is filtered by the kidney and then the filtered glucose is either reabsorbed by the kidney or excreted in the urine. Glucose uptake is essential for energy requirement and the newly synthesized glucose via gluconeogenesis is also released into the circulation (Marsenic 2009). Unfavorable changes in the kidney tissue are usually generated due to metabolic syndrome, obesity, and diabetes leading to altered kidney function.

The main cause of chronic kidney disorder (CKD) is hyperglycemia that can lead to diabetic nephropathy, which in turn is main cause of end-stage renal ailment (Rebić et al. 2015).

Recent research has proved to be beneficial in comparing hypoglycemia and antihyperlipidemic consequences of lyophilized *C. intybus* seed extract (CSE). One of the study proposed the usefulness of CSE in preventing diabetes-induced kidney damage (McMahon and Waikar 2013). Another study was carried out on diabetic animals with early type 2 diabetes and late type 2 diabetes. In early type 2 diabetes, CSE was found to possess ameliorating effects on urea, BUN, alpha-1-microglobulin, sodium, and potassium in serum. One more study evaluated the urine of early type 2 diabetes after using *Cichorium* seed extract and the promising effect was observed on the levels of alpha-1-microglobulin, as urine alpha-1-microglobulin was substantially reduced. In yet another study serum uric acid levels decreased in late type 2 diabetes by using *C. intybus* seed extract. Hence, from both the studies it can be concluded that the *C. intybus* benefitted each kind of diabetes with reference to histology-reduced glomerular diameter and serum uric acid in late type 2 diabetes and lowered urinary alpha-1-microglobulin in early type 2 diabetes (Ghamarian et al. 2012).

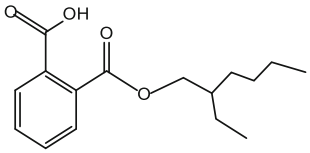
12.6 Phytochemistry

Phytochemical screening of *C. intybus* revealed that various parts of the plant contain different constituents such as sesquiterpene lactones, derivatives of caffeic acid like chicoric acid, chlorogenic acid, isochlorogenic acid, and dicaffeoyltartaric acid), inulin, proteins, sugars, flavonoids, alkaloids, coumarins, hydroxy derivatives of coumarins, terpenoids, essential and volatile oils, polyenes, and numerous vitamins (Al-Snafi 2016). The structures of various isolated compounds have been shown in Fig. 12.1.

12.6.1 Phytochemistry of Root

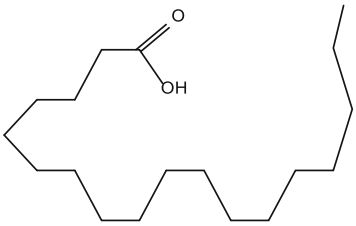
A study was conducted to isolate numerous compounds from the roots of the plant. Upon transformed root culture, sesquiterpenes of germacrane and guaiane type such as lactucopicrin, 8-desoxylactucin were isolated from the roots along with glycosides of sesquiterpene lactone (sonchuside A, ixerisoside D, and crepidiaside B). Chicory roots contained higher amount of tannins but lesser total phenolic content.

The methanolic extract of chicory root was studied using GC-MS chromatographic technique, which reveals the presence of 22 compounds that were later identified and exhibits several peaks indicating the presence of different characterized constituents using National Institute of Standards & Technology (NIST) library database. The major group in these compounds was aldehyde, fatty acid, hydrocarbon, ester, steroid, and terpenoid and the compounds which were

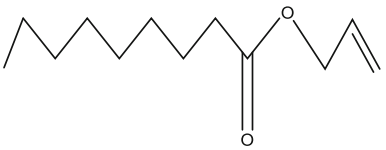


1, 2-Benzenedicarboxylic acid, mono (2-ethylhexyl) ester

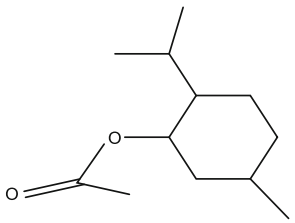
2,4-decadienal 2-Furancarboxaldehyde



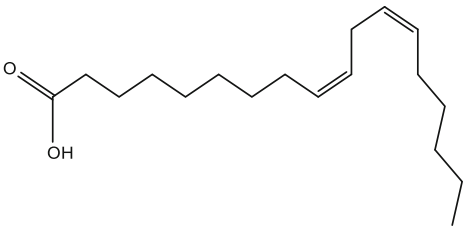
Octadecanoic acid



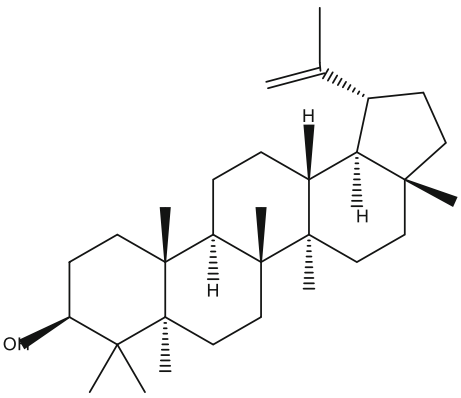
2-propenyl nonanoate



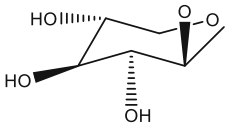
Cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate



9,12-Octadecadienoic acid (Z, Z)

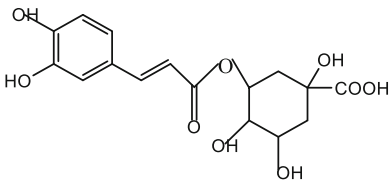


Lupeol

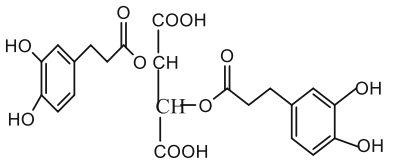


? - D-Glucopyranose, 1,6-anhydro-

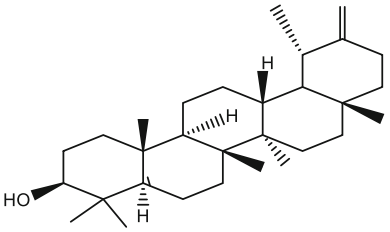
Fig. 12.1 The structures of some chemical constituents from *C. intybus* extract using HPLC



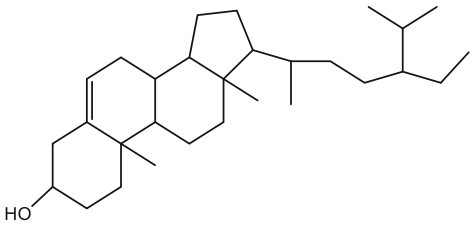
Chlorogenic acid



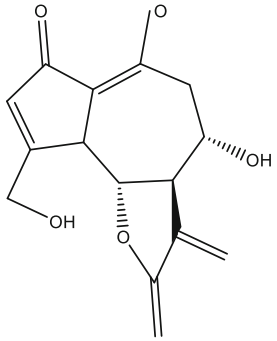
2S,3S-O-Dicaffeoyl tartaric acid
(chicoric acid)



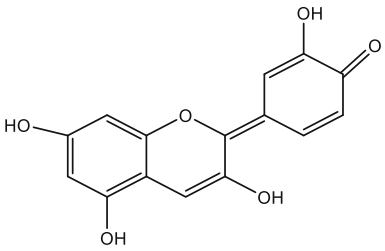
alpha -Lactucerol



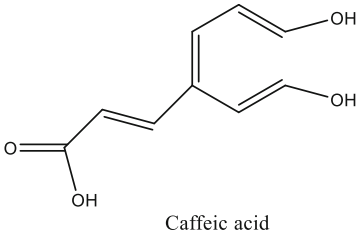
beta-Sitosterol



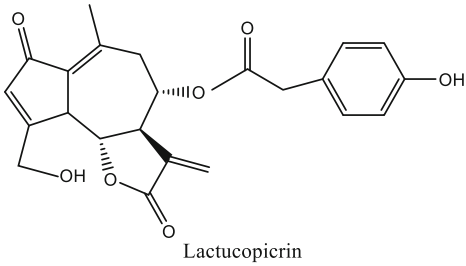
Lactucin



Cyanidin

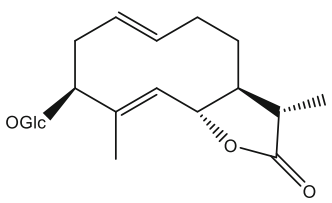


Caffeic acid

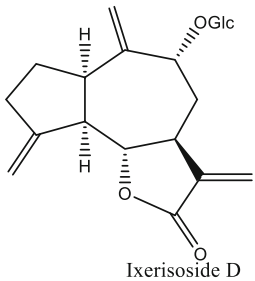


Lactucopicrin

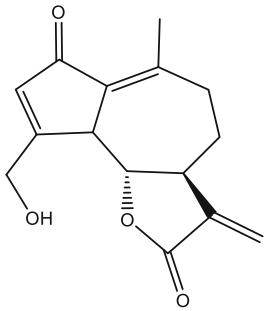
Fig. 12.1 (continued)



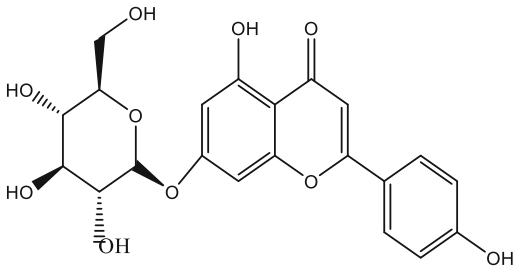
Sonchuside C



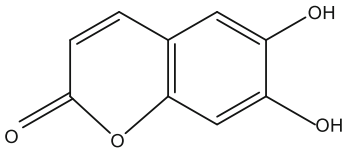
Ixerisoside D



8-Deoxylactucin



Apigenin 7-glucoside



Cichorin

Fig. 12.1 (continued)

identified include tetradecanoic acid; 2-(ethylhexyl)salicylate; 1,2-benzenedicarboxylic acid; bis(2-methylpropyl)ester; 2-decenal (Z); 2,4-decadienal (E,E); 9-octadecenoic acid; hexadecanoic acid; cis-9-Hexadecenoic acid; *n*-hexadecanoic acid; octadecanoic acid; eicosatrienoic acid (Z,Z,Z), mono (2-ethylhexyl)ester; cyclopropane; hexadecane; 1,1-dichloro-2,2,3,3-trimethyl-9,12 octadecadienoic acid (Z,Z); 2-hydroxy-1-(hydroxymethyl)ethylester; docasone; stigmasta-dien-3-ol; beta-sitosterol; lupeol (Malik et al. 2016).

Other studies conducted on chicory root reveal the presence of several phytoconstituents like inulin (a polysaccharide similar to starch), flavonoids, coumarins, sesquiterpene, lactones (e.g., lactucopicrin and lactucin), tannins, vitamins, minerals, alkaloids, and volatile oils. Inulin, a fructose polymer with beta

glycosidic linkage, is contained in 68% of compounds isolated from chicory roots (Nwafor et al. 2017). A study conducted by Soobo reported that root of chicory is high in oligofructose and fructan-containing inulin (Shim 2005). Chemically inulin has been converted to two fragments, that is, glucose and fructose by the process of hydrolysis as it is a polydisperse(2,1) fructan (Peters and van Amerongen 1998). Numerous sesquiterpenes are found to be accountable for the bitter taste of chicory and this was confirmed by isolating sesquiterpene lactones like lactucin, 8-deoxylactucin and lactucopicrin. One more study on roasted chicory roots reported that it contain various other compounds like phenols, furfural, vanillin, pyrazine, benzothiazoles, aldehydes, phenyl acetic acid, 2-acetylpyrrole, furans, aromatic hydrocarbons, organic acids, and insole alkaloid (like carboline) in traces (de Kraker et al. 1998). Chicory root extract in which the insoluble fraction was removed using filtration and centrifugation was found to contain alkaloids, volatile oils, fixed oils, fatty acids (oleic and palmitic acid),triterpenes, tannins, sugars (mannose and fructose), and saponins (Nandagopal and Kumari 2007).

12.6.2 Phytochemistry of Flower

For the study of phytoconstituents present in the flower of chicory, the technique of column chromatography was used. The study conducted by Norbaek used subsequent preparative HPLC with Amberlite XAD-7 for carrying out column chromatography which isolated anthocyanins from the plant (Nørbæk et al. 2002).

In yet another study, the methanolic extract of chicory flower was evaluated using GC-MS technique and hence different bioactive compounds were identified, some of the important bioactive compounds include ketones (4h-pyrone; 4-(1-hydroperoxy-2,2-dimethyl-6-methylene-cyclohexyl)-pent-3-en-2-one; 6-Dodecanone, 2-Heptadecanone); Aldehyde (5-(hydroxymethyl)-2-furaldehyde), Fatty acids (octadecanoic acid, tetradecanoic acid, *n*-hexadecanoic acid and heptadecanoic acid); hydrocarbons; esters (2-propenyl nonanoate, cyclohexanol, etc.), sugar, steroids (Malik et al. 2016).

One more study proposed that the flowers also contain cichoriin in addition to intybin, lactucin, and a crystalline colorless glucoside (Shaikh et al. 2010). Saccharides, methoxy-coumarin cichorine, essential oils, and flavonoids were also found to be present in chicory flowers (Street et al. 2013).

12.6.3 Phytochemistry of Seed

The study on phytochemical evaluation on seeds of the plant reported that the chicory seed extract contained significant amount of phenolics content (51.7–284 GAE mg/100 g of dry sample) and flavonoids (42.2–152 CE mg/100 g of dry sample) (Al-Snafi 2016).

From analysis of Bisma Malik, the major compounds that are present in the seed extract are fatty acids (pentadecanoic acid, *n*-hexadecanoic acid, tetradecanoic acid, octadecanoic acid, and 9-octadecenoic acid); esters (1,2-benzenedicarboxylic acid,

bis(2-methylpropyl) ester, hexadecanoic acid, methyl ester, 9,12-octadecanoic acid); hydrocarbons (octacosane, docosane); terpenoids (verrucarol, lupeol); steroids (stigmasterol), and ketones.

According to the study of (WenYing and Jin-Gui 2012), chicory seeds are rich of nutrients which are beneficial for two types of nutrition, that is, monogastric and ruminant. They also determined that most chicory seed varieties possess crude protein in higher amounts which usually more than 19% of dry weight and these chicory seeds are 1.5–2.5 times more efficient than the standard grains, like rice, barley, corn, and wheat. These authors distinguished that chicory seeds are also considered to be the reliable source of nearly all essential amino acids like leucine, methionine, phenylalanine, lysine, isoleucine, etc.

In addition, the seeds are also considered to be the good source of saturated as well as unsaturated fatty acids of which linoleic acid, including monounsaturated acids like oleic acid, stearic acid, and palmitic acid is about 76%. On comparison with other plant parts, the seeds are found to be the main source of vital minerals like potassium, selenium, magnesium, zinc, and calcium. Moreover, from *C. intybus* seeds, some researchers have isolated a sesquiterpene glycoside, cichotyboside, which had been confirmed to possess a good hepatoprotective activity. From the above discussion it can be concluded that the chicory seeds are essential nutritional components for both humans as well as animals (WenYing and Jin-Gui 2012).

12.6.4 Phytochemistry of Stem

A number of compounds such as tannins, flavonoids, saponins, cardiac glycosides, terpenoids, and anthocyanins were seen in the stem of *C. intybus* after phytochemical analysis (Al-Snafi 2016). By using GC-MS different phytochemicals were identified and characterized by using NIST library database. The important phytochemicals identified from the stem of *C. intybus* are fatty acids (tetradecanoic acid, *n*-hexadecanoic acid, pentadecanoic acid); aldehydes (2-furancacarboxaldehyde, 5 (hydroxymethyl)palmitaldehyde); sugar (beta-D-glucopyranose,1,6 anhydro); terpenoid (2-hexadecen-1-ol, lupeol, etc.); hydrocarbons; steroids (cholesta(4,6-dien)3-ol, acetoxystigmasta-4,6,22-triene, stigmasterol, gamma-sitosterol), and esters (Malik et al. 2016) (Table 12.1).

12.6.5 Phytochemistry of Leaf

The phytochemical analysis on the leaves of *C. intybus* conducted by (Al-Snafi 2016) reported that the total flavonoid content and total phenolic content is comparatively high than other parts of the plant and it was also determined that leaves have comparatively high reducing sugar and nonreducing sugar content. Chicory leaves are also considered to be rich source of usually free amino acids and proteins that are soluble in water. The list of identified compounds from methanolic extract of leaf as well as root using HPLC technique are given in Table 12.2.

Table 12.1 Traditional uses of various parts of plant *Cichorium intybus*

Plant part	Traditional use	Reference
Seeds	Disorders of liver	Ahmed et al. (2003)
Root	Jaundice	Pushparaj et al. (2007)
	Enlargement of liver	
	Gout	
	Rheumatism	
	Relief of cough	
	Diabetes	Ahmed et al. (2009)
	Arteriosclerosis	Loi et al. (2005)
	Anti-arthritis	
Leaves	Cleansing of blood	Pieroni (2000)
	Reduction of blood pressure	Guarrera et al. (2005)
	Antispasmodic	Loi et al. (2005)
	Wound healing	Sezik et al. (2001)
Stem	Jaundice	Van Wyk et al. (1997)
	Stimulant	
Whorls	Depurative	Pieroni et al. (2002)
Aerial part	Cholagogue	Kokoska et al. (2002)
	Digestive	
	Renal	Jouad et al. (2001)
Whole plant	Eupeptic	Miraldi et al. (2001)
	Choleretic	
	Laxative	
	Stomachic	
Flower	Diarrhea	Šavikin et al. (2013)

Table 12.2 Compound identification in *Cichorium intybus* extract using HPLC Mona et al. (2009)

Cichorium intybus	Methanolic extract (%)	Total phenolic content (%)	Phenolic compound
Roots	10.75	20.0 ±0.9	Caffeic acid m-Coumaric acid Protocatechuic acid p-Coumaric acid Chlorogenic acid
Leaves	23.16	26.4±1.05	Isovanillic acid Protocatechuic acid p-Hydroxybenzoic acid Caffeic acid Chlorogenic acid p-Coumaric acid

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Phytochemical and Pharmacological Properties of *Picrorhiza kurroa*

13

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Abstract

Picrorhiza kurroa of family Scrophulariaceae represents an endangered, small, hairy perennial medicinal herb indigenous to India, which grows in subalpine Himalayan province wild from Kashmir to Sikkim at an elevation of 3000–5000 m. It has got a wide range of medicinal properties which are attributed to presence bioactive phytoconstituents, like cucurbitacins, Picroside I and II, and phenolic components. As per various reports, the plant has been used traditionally and possesses significant antioxidant activity, and thus could be potentially

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helpful in the management of cancer, diabetes mellitus, and liver diseases. Besides, numerous studies have shown that Picrorhiza has got tremendous cardioprotective, anti-inflammatory, antimicrobial, immunomodulatory, and anti-malarial activity which are attributed due to the presence of kutkin, a principal active constituent of this plant. This chapter is an attempt to compile detailed literature available on scientific researches of phytochemical constituents, and pharmacological properties of the *P. kurroa.*

Keywords

Picrorhiza kurroa · Kutki · Phytoconstituents · Biological activities · Clinical trial

13.1 Introduction

Picrorhiza kurroa Royle ex. Benth (*P. kurroa*) also known as kutki, and Indian gentian, a member of Scrophulariaceae family, is an endangered, small, hairy, everlasting medicinal plant indigenous to India. It grows wild in Himalayan province ranging from Kashmir to Sikkim at an elevation of 3000–5000 m (Bhattacharjee et al. 2013; Soni and Grover 2019). It is chiefly found in Nepal's western region where it grows in the crevices of rock, facing slopes on the north, typically on cliffy and sloppy mountains cliffs and the turf of glacial flats. It is distributed from Kashmir to Kumaon in Himalayan region and Nepal to Garhwal north Burma, west China, and Southeast Tibet (Chhetri et al. 2005). Traditionally, it is known very well in Indian Ayurvedic system, in which mainly roots and rhizomes are used for the management of liver diseases, chronic fever, indigestion, cardiac ailments, and diarrhea (Bhandari et al. 2010; Dwivedi et al. 1992). International Union for Conservation of Nature and Natural Sources has declared *P. kurroa* as an endangered species because of its overutilization from natural habitat and has been included in Appendix II of the Convention on International Trade in Endangered Species (CITES) list (Bhat et al. 2012; Nayar and Sastri 1990). Its principal active constituent kutkin, constitutes Picroside I and II and the kutkoside (Bhandari et al. 2009; Sah and Varshney 2013). Small doses of *P. kurroa* mainly dried roots and rhizomes are used for stimulating appetite, stomachache, in small quantities as a laxative, and as purgative (Arya et al. 2013). In India, it is listed among top 15 species which are sold for its economic value (Ved and Goraya 2007). Approximately 500 tons of this plant are demanded globally per year and out of the total supply of 375 tons, only 75 tons/year is contributed alone by India (Thani 2018). Due to the presence of higher moisture content, materials collected in July and August is low rated, while materials collected in the month of September is high rated due to low moisture content. To fulfil the herbal drug industries demand, *Picrorhiza* is collected mostly from Sikkim, Uttarakhand, Kashmir, and Himachal Pradesh (Arya et al. 2013; Debnath et al. 2020; Uniyal et al. 2011).

Table 13.1 Taxonomical classification

Rank	Scientific name and common name
Kingdom	Plantae-plants
Phylum	Tracheophyta
Class	Dicotyledonae
Subclass	Asteridae
Order	Lamiales
Family	Scrophulariaceae-figwort
Genus	Picrorhiza
Species	*Picrorhiza kurroa*—Kutki, kadu, hellebore

13.1.1 Taxonomy

Binomial name: *Picrorhiza kurroa* Royle ex. Benth.

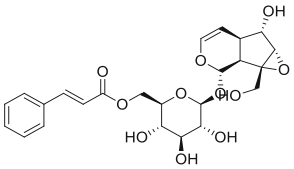
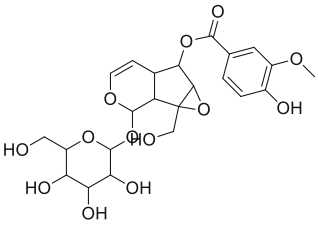
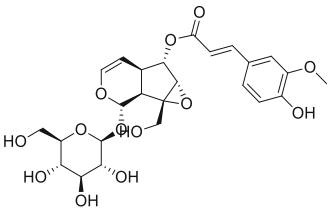
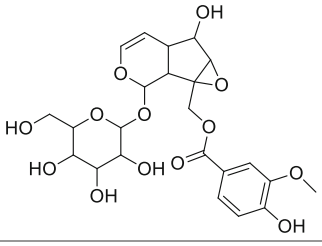
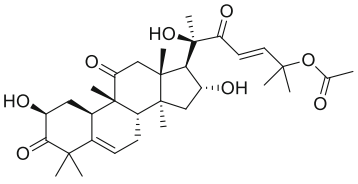
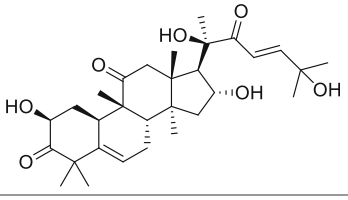
Synonym: *Picrorhiza lindleyana* (Wall.) Steud.

Around 200 genera and 3000 species of *Picrorhiza* (Table 13.1) are recognized in family Scrophulariaceae, which are mostly distributed in temperate regions of the world. *P. kurroa* is an everlasting plant with a slender, creeping rhizome along with basal and alternate leaves (5–10 cm in length) having a sharp apex. The flowers are present on a long spike which are either white or pale purple in color. The calyx splits up into five parts equally, and the corolla has got four to five lobes, 4–5 mm long with capitate stigma. Fruits are oval-shaped, tapered at the top, and 12 mm long with numerous ellipsoid seeds, along with transparent and thick seed coat. The rhizomes are thick, subcylindrical, or curved; grayish-brown in color externally; and presence of spherical scars of roots and furrows makes external surface coarse in texture. Root is elongated, tubular, straight, or curved marginally associated mostly with rhizomes. The flowering period of *Picrorhiza kurroa* (PK) is June to August.

13.2 Phytochemistry of *P. kurroa*

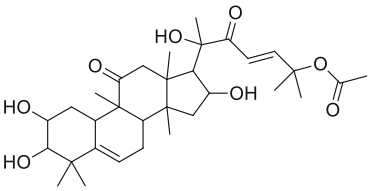
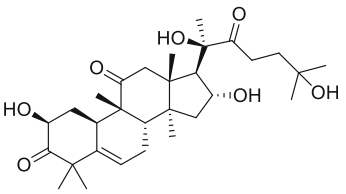
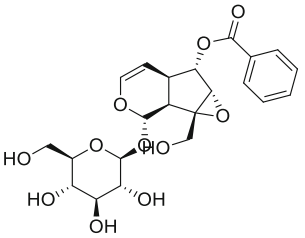
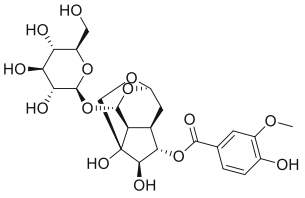
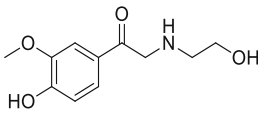
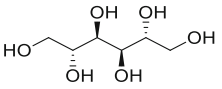
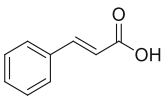
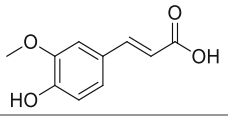
The phytochemical composition of PK has been widely researched and numerous studies have contributed to the discovery of 132 active ingredients from various parts of plant, including leaves, roots, branches, and seeds. An essential category of bioactive compounds of PK isolated (Table 13.2) from rhizomes are kutkoside, picroside I–III, and cucurbitacin, and elucidated by high-performance liquid chromatography (HPLC). Phytoconstituents like 4-hydroxy-3-methoxy acetophenone, pikuroside, veronicoside, and numerous phenolic compounds are also found in various extracts of PK (Sharma et al. 2012). Many other active compounds substances derived from PK include apocynin and drosine (Simons et al. 1989). *P. kurroa* consists of cucurbitacins that are known for having antitumor properties (Salma et al. 2017). Rhizomes of PK also contain kutkoside and glycosides. It also documented the occurrence of pikurosides, picrosides (I–IV), kutkosides, and flavonoids viz. vanillic acid and apocynin in the 70% hydroalcoholic fraction.

Table 13.2 Some essential bioactive compounds isolated form *Picrorhiza kurroa*

Phytoconstituent	Structure	References
Picroside I		Kitagawa et al. (1969), Weinges et al. (1972)
Picroside II		Singh and Rastogi (1972)
Picroside III		Weinges (1977)
Kutkoside		Singh and Rastogi (1972)
Cucurbitacin B		Laurie et al. (1985), Salma et al. (2017), Stuppner and Wagner (1989)
Cucurbitacin D		

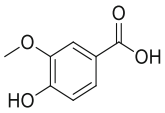
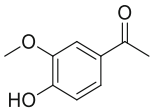
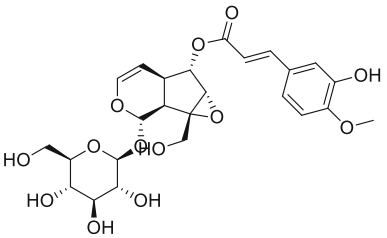
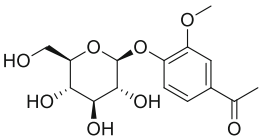
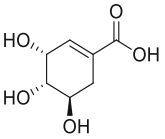
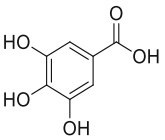
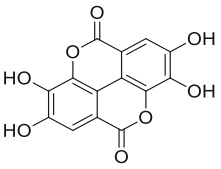
(continued)

Table 13.2 (continued)

Phytoconstituent	Structure	References
Cucurbitacin Q		
Cucurbitacin R		
Veronicoside		Stuppner and Wagner (1989)
Pikuroside		Jia et al. (1999)
4-Hydroxy-3-methoxy acetophenone		Sharma et al. (2012)
D-mannitol		Kumar et al. (2013)
Cinnamic acid		Kumar et al. (2013)
Ferulic acid		Kumar et al. (2013)

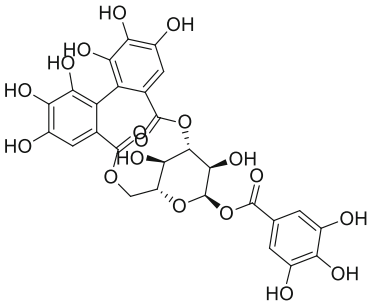
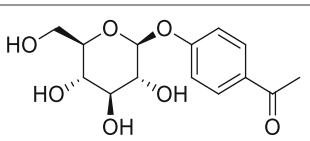
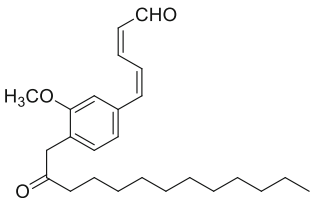
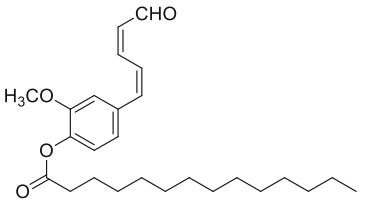
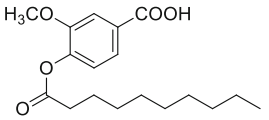
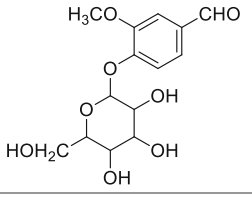
(continued)

Table 13.2 (continued)

Phytoconstituent	Structure	References
Vanillic acid		Rastogi et al. (1949)
Apocynin		Basu et al. (1971)
Minecoside		Stuppner and Wagner (1989)
Androsin		Stuppner and Wagner (1989)
Shikimic acid		Zhang et al. (2004)
Gallic acid		Zhang et al. (2004)
Ellagic acid		Zhang et al. (2004)

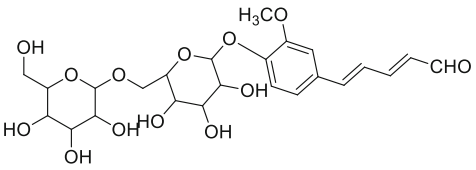
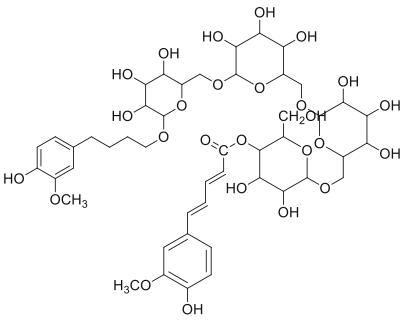
(continued)

Table 13.2 (continued)

Phytoconstituent	Structure	References
Isocorilagin		Zhang et al. (2004)
Picein		Stuppner and Wagner (1989)
Lauryl picraldehyde		Ali et al. (2017)
Myristyl picraldehyde		
Capryl vanillic acid		
Vanillin-α-D-glucoside		

(continued)

Table 13.2 (continued)

Phytoconstituent	Structure	References
Picraldehyde diglucoside		
Picrortetra-glucoside		

Other essential phytoconstituents derived from the PK are carbohydrates and aromatic acids (Kumar et al. 2013).

13.3 Pharmacological Activities of *P. kurroa* (PK)

Numerous pharmacological activities attributed to the presence of various phytoconstituents have been reported from the *P. kurroa* (Fig. 13.1).

13.3.1 Cardioprotective Effect of *P. kurroa*

Cardiovascular disease (CVD) is a blanket term for a group of pathological conditions involving cardiovascular system. It includes coronary heart disease, congenital heart disease, rheumatoid heart disease, peripheral arterial disease, cerebrovascular disease, etc. The various risk factors associated with the development of CVDs are obesity, dyslipidemia, diabetes, smoking, and hypertension (Stewart et al. 2017). CVD is a major concern in diabetic patients as it is a major cause of deaths among these people (Einarson et al. 2018).

Nandave et al. authenticated *P. kurroa* extract (PK) against cardiotoxicity induced by isoproterenol in male Wistar rats. Pretreatment with 200 mg/kg of an extract decreased the lipid peroxidation markedly. It preserved the cell membrane stability and integrity that consequently reduced the passage of enzymes in plasma, which are the hallmark of myocardial damage. The cardioprotective effect is due to the antioxidant effect of the extract (Nandave et al. 2013).

Fig. 13.1 Pharmacological activities reported from *P. kurroa*

Ethanolic extract of PK displayed reasonable protection against Adriamycin-challenged cardiomyopathy in male albino Wistar rat. The *Picrorhiza* (50 mg/kg) on oral administration daily for 15 days demonstrated the significant cardioprotective effect by decreasing lactate dehydrogenase (LDH), creatine phosphokinase (CPK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels in plasma and also prevents lipid peroxidation, which leads to the membrane instability and damage to heart tissue. Furthermore, the antioxidative enzyme profile was significantly increased as indicated by enhanced levels of superoxide dismutase, catalase, etc. Hence, the *Picrorhiza* efficiently alleviated all the harmful effects triggered by Adriamycin and preserved the myocardial membrane integrity and oxidative damage by strengthening the antioxidant mechanism in myocardial tissue (Rajaprabhu et al. 2007).

13.3.2 Antidiabetic Effect of *P. kurroa*

Diabetes mellitus (DM) happens to be one of the oldest, serious, and chronic disease governed by increased blood sugar levels resulting from either failure in production of insulin or increase in the insensitivity of the tissues toward insulin (Tan et al. 2019). The classic diabetic symptoms include polyuria (excessive urine passage), polyphagia (increased hunger), and polydipsia (intense thirst) (Ramachandran 2014). Diabetes is linked to multiple macrovascular and microvascular complications such as neuropathy, retinopathy, nephropathy, cardiovascular complications (like myocardial infarction), and cerebrovascular diseases (stroke) (Forbes and Cooper 2013).

Joy and Kuttan researched antidiabetic activity of hydroalcoholic extract of *P. kurroa* using Wistar albino strain of rats. The extract has been shown to diminish the level of glucose. *Picrorhiza* extract (75 and 150 mg/kg) administered orally considerably reduced the blood glucose level over 10 days in alloxan-induced diabetes in rats. A 75 mg/kg dose reduced the blood sugar by 43%, while 60% reduction was observed with 150 mg/kg. The levels of urea in blood and lipid peroxides as an indicator of kidney and liver injury respectively was assessed, and a significant decrease was observed with *Picrorhiza* extract–treated animals in comparison to diabetic control groups (Joy and Kuttan 1999).

In a study done by Husain et al., where they administered aqueous extract of PK, in streptozotocin–nicotinamide-induced diabetic rats administered orally at doses of 100 and 200 mg/kg for 14 days elevates insulin levels in plasma. Histopathological examination revealed the more population of β pancreatic cell in *Picrorhiza*-treated group as compared to the diabetic control group (Husain et al. 2014).

Administration of aqueous extract of PK via oral route in streptozotocin–nicotinamide-induced rats at of 100 or 200 mg/kg dose for 2 weeks markedly reduced the fasting glucose levels and hence enhanced the glucose tolerance. The glycogen level in all the groups was compared, and *Picrorhiza* was found to restore the reduced levels of glycogen in liver, which is an indication of enhancement in the liver glycogenesis. The *Picrorhiza* extract also reversed the weight loss observed in diabetic rats (Husain and Singh 2009).

Chauhan et al. examined the antidiabetic activity of alcoholic and aqueous extract of PK rhizome at a concentration of 250, 500 mg/kg for 15 days in alloxan-induced diabetes in Wistar albino rats. The *Picrorhiza* extract–treated group showed decreased levels of glycosylated hemoglobin (HbA_{1C}) and blood sugar. Furthermore, increase in the levels of insulin in plasma and hemoglobin content was noticed in extract-treated group. Also, reduction in oxidative stress markers, such as malondialdehyde (MDA), peroxide, superoxide and nitric oxide radicals, and increase in antioxidant profile, that is, catalase (CAT), superoxide dismutase (SOD), glutathione oxidase, and glutathione-S-transferase, was associated with *Picrorhiza* extract treatment group. Moreover, the decrease in the weight of animals in diabetes animals was brought to normal by *Picrorhiza* (Chauhan et al. 2008).

Immune-mediated destruction of pancreatic beta cells decreases the efficiency of these cells and hence resulted in diabetes mellitus. Therefore, regeneration of the beta cell is one of the promising approaches to tackle the disease. Kumar et al. showed the antidiabetic effect of hydroalcoholic extract of PK on autoimmune diabetes mellitus elicited by streptozotocin in male Wistar rats. The hydroalcoholic extract decreased the blood glucose level and demonstrated significant ability to regenerate the pancreatic β cells and has the potential to cause insulin release. Alterations in ST, ALP, SOD, ALT, and catalase levels were normalized. The extract showed efficacy toward streptozotocin-mediated β-cell destruction and also showed an inhibitory effect on glucagon signaling through suppressing the expression of glucagon receptor in liver and kidney tissues and results in hypoglycemia. The hypoglycemic effect is due prevention of glucagon binding to these receptors, which is responsible for gluconeogenesis and glycogenolysis. The extract also

enhances the proliferation of Rin5f cells (insulin-producing cells) and increases the cellular uptake of glucose (Kumar et al. 2017).

13.3.3 Hepatoprotective Effect of *P. kurroa*

Various essential physiological functions of metabolism, storage, and secretion are mainly operated through liver. Hepatic disorders are highly prevalent disease and death, causing disorder in the world (Khan et al. 2019). Hepatotoxicity is caused by various agents such as viruses, parasites, environmental pollutants, alcohol abuse, and chronic administration of drug that leads to the development of various hepatic disorders including cirrhosis, alcohol liver disease (ALD), hepatitis B & C (HCC) (Khan et al. 2019; Saha et al. 2019; Shakya 2020). The various pathways involved in pathogenesis of hepatotoxicity are cell membrane destruction, modulation of various cellular pathways involved in metabolism of drugs, activation of immune system response, free-radical accumulation, inflammation, lipid peroxidation, and subsequently cell death (Cichoż-Lach and Michalak 2014; Del Campo et al. 2018; Khan et al. 2019; Mohi-Ud-Din et al. 2019).

Sinha et al. examined the hepatoprotective effect of aqueous extract of *P. kurroa* in vitro, utilizing mouse liver slice culture harvested from the liver of mice. The hepatotoxicity was induced using alcohol. The extract decreases the lipid peroxidation as indicated by decrease in the MDA products. The elevated lactate dehydrogenase (LDH), serum glutamic pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT) levels of liver damage markers were inhibited. Furthermore, antioxidant enzyme activities was found to be increased (Sinha et al. 2011).

The rhizome extract of PK in combination with honey demonstrated fruitful results against acetaminophen-induced liver toxicity by altering the activity of hepatic enzymes and synergistically function in boosting the hepatoprotection and hepato-regeneration ability in liver toxicity. Histopathological study revealed that either *Picrorhiza* or honey alone or as combinational approach exhibit reduction in the deleterious effect of acetaminophen. Furthermore, the elevated levels of SGOT and SGPT in the injured liver were also normalized (Gupta et al. 2016).

Dwivedi et al. performed an experiment to evaluate the protective effect *Picrorhiza* extract (12.5 and 25 mg/kg) in thioacetamide-induced hepatic injury and concluded that the extract was equally effective in reducing the enhanced levels of serum SGOT and SGPT as that of silymarin. Moreover, the level of alkaline phosphatases was also reduced but no effect was observed on the bilirubin. Increase in the levels of δ-glutamyl transpeptidase and decrease in succinate dehydrogenase and glucose 6-phosphatase were observed (Dwivedi et al. 1991).

Picrorhiza extract has also been reported as an anti-hepatoxic agent against carbon tetra chloride (CCl_4)–induced injury in mice. The results from the experiment revealed that the less alterations in the levels of alanine aminotransferases (ALT), alkaline phosphatase (ALP), reduced glutathione (GSH), catalase (CAT), and Na+/K

+ ATPase after *Picrorhiza* administration. The histological studies showed decrease in liver lesions in extract-treated group (Santra et al. 1998).

The *P. kurroa* hydroalcoholic extract exhibited considerable hepatoprotective effect in against high fat diet (HFD)-induced nonalcoholic fatty liver disease (NAFLD) at a dose of 200 and 400 mg/kg for a duration of 4 weeks. The extract reduced the ALT and ALP levels and also decreased the lipid content of liver in the treatment group. Histopathological examination revealed that treatment with PK extract showed minimal damage to liver and maintains the structure and morphology of the liver (Shetty et al. 2010).

The other studies that established the hepatoprotective activity of PK against various adversities like exposure to aflatoxin B1 (Dwivedi et al. 1993), cadmium (Yadav and Khandelwal 2006), galactosamine (Dwivedi et al. 1992), alcohol (Rastogi et al. 1996), oxytetracycline (Saraswat et al. 1997), and monocrotaline (Dwivedi et al. 1991) have been reported.

13.3.4 Anticancer Effect of *P. kurroa*

Cancer is a global concern, responsible for eight million deaths annually, and is predominantly prevailing in developing nations as about 63% deaths are outlined due to cancer from these countries (Abbas and Rehman 2018; Wani et al. 2021). Cancer development is a multistep process which involves three phases: initiation, promotion, and progression (Chakravarthi et al. 2016), resulting from modifications at genetic and epigenetic level by altering various signaling pathways (Li et al. 2020; Trosko 2005).

A research was conducted to investigate the anticancer property of extract of rhizome of PK (both alcoholic and aqueous) on multiple cell lines namely (MDA-MB-435S), (Hep3B), and (PC-3). The study concluded the potential cytotoxicity of the extract in all the cell lines trough induction of apoptosis. Ferric ion-reducing antioxidant power (FRAP) and thiobarbituric acid (TBA) assays revealed the radical scavenging property of both alcoholic and aqueous extract with maximum effect exhibited by aqueous extract of *P. kurroa* (Rajkumar et al. 2011b).

Anticancer activity of Picroliv, an important constituent obtained from root extract of PK, was explored in Sprague Dawley rat subjected to 1,2-dimethylhydrazine hydrochloride (DMH). The oral administration of different doses (40 and 200 mg/kg) of Picroliv showed promising result in liver carcinogenesis and liver necrosis. The elevated level of liver g-glutamyl transpeptidase (Y-GT), a marker of neoplastic events induced by DMH gets reduced in Picroliv treatment group. Normalization of the levels of catalase and superoxide dismutase and reduction in lipid peroxidation was found with Picroliv administration (Rajeshkumar and Kuttan 2003).

Rajeshkumar and Kuttan (2000) identified the antitumor potential of Picroliv against N-nitrosodiethylamine (NDEA) prompted liver cancer in mice model. Orally given Picroliv (200 mg/kg) reduced the raised gamma-glutamyl transpeptidase

(gamma-GT) levels in liver and plasma at a comparable level as that of normal group. Also, the substantial reductions in increased levels of ALP, serum peroxidases, and bilirubin was observed in Picroliv treatment group (Rajeshkumar and Kuttan 2000).

Methanolic extract (75%) of PK (150 and 750 mg/kg orally) in Swiss albino mice resulted in inhibition of sarcoma induced by administration of 20-methylcholanthrene. Dose-dependent reduction in volume of implanted solid tumor was observed and increase in survival ascites tumor–bearing mice. *Picrorhiza* extract also demonstrated inhibitory effect on topoisomerase I and II in *S. cerevisiae* mutant strain cell culture; however, no effect was observed with cdc2 kinase, which is an enzyme that regulates cell cycle (Joy et al. 2000).

Rathee et al. conducted a study on (MCF-7) to explore the anticancer property of *Picrorhiza* extract and Kutkin, Picroside I, and Kutkoside. Treatment with this extract showed potential cytotoxicity in a dose-dependent pattern. The extract and isolated glycosides possessed anti-invasive and anti-migratory effect through suppression of metalloproteases, matrix metalloproteinase 2 (MMP-2), 9 (gelatinases) and MMP-1, 13 (collagenases) that are involved in the process (Rathee et al. 2013).

Evaluation of picroside II, an iridoid glycoside obtained from PK, revealed its antimetastatic, and antiangiogenic properties. The matrix metalloproteinase 9 (MMP-9) is an important player responsible for cancer metastasis through degradation of extracellular matrix was reduced. Also, the angiogenic marker, cluster of differentiation (CD31) was also suppressed (Lou et al. 2019).

13.3.5 Immunomodulatory Effect of *P. kurroa*

For protection from various infections and pathogens in humans, immune system plays an important role. Innate and adaptive systems are the two branches of immune system, among which the innate immune functions with distinct mechanism for protection against pathogen, while the nonadaptive trigger the stimulation of antimicrobial defense mechanism by sensing pathogen through well-recognized receptors. However, the relation between various immune components is not fully understood (Turvey and Broide 2010).

Amit et al. evaluated biopolymeric fraction RLJ-NE-205 isolated from *P. kurroa* rhizomes for immunomodulatory effect and studied parameters like phagocytic index, HA titre, DTH reaction, PFC assay, proliferation of lymphocytes, and analysis of cytokines in serum. Pretreatment with 50 mg/kg fraction RLJ-NE-205 significantly increases lymphocytes and cytokine levels in serum and significantly strengthens the immune system (Gupta et al. 2006).

Arshad et al. examined the immunomodulatory response of ethanolic and aqueous extract of PK against cyclophosphamide-induced immunosuppression in rats. The immunomodulatory effect was authenticated by studying humoral antibody response to sheep red blood cells (SRBC) and was concluded that both the ethanolic and aqueous extract of PK showed significant increase in delayed type hypersensitivity response among which ethanolic extract was more potent (Hussain et al. 2013).

In another study, an experiment was carried out to evaluate the immunomodulatory activity of *P. kurroa*, *Asparagus racemosus*, and *Withania somnifera*, against cyclophosphamide immunosuppressive agent in male Swiss albino mice. The finding of this experiment uncovered that all these herbs demonstrated footpad thickness in Delayed Type Hypersensitivity (DTH). The results further revealed that among all the three herbs, *W. somnifera* enhances humoral antibody response (Siddiqui et al. 2012).

Sharma et al. evaluated the immune-stimulatory activity of *P. kurroa* leaf extract against sheep RBC (SRBC)–induced hypersensitivity reaction in mice serum. Pretreatment with 50% ethanolic extract of PK significantly elevates humoral and cell-mediated components of the immune system in mice and rats and also stimulate the phagocytosis in reticuloendothelial cells of mice (Sharma et al. 1994).

The root and rhizome extract of PK (Picroliv) in combination with paromomycin and miltefosine revealed fruitful results used against *Leishmania donovani*/hamster model. The results of this study revealed that the antileishmanial efficacy and lymphocyte proliferation was significantly enhanced by Picroliv on combination with paromomycin and miltefosine and thus was concluded that Picroliv can be used as adjunct to anti-leishmanial chemotherapy (Sane et al. 2011).

13.3.6 Antimicrobial Effect of *P. kurroa*

Antimicrobial means potency of drugs or chemical by virtue of which they can kill or inhibit the growth of disease causing microbes and may be classified as antibiotics, antifungal, or antiviral based on the microorganism primarily they act against (Salma et al. 2017).

Vinoth et al. authenticated the antimicrobial activity of acetone, ethanol, methanol, aqueous, and hexane extract of *P. kurroa* against selected gram-negative and gram-positive bacterial strain. The result of the study demonstrated that ethanolic extract of PK rhizome possesses significant antimicrobial activity against *K. pneumoniae*, *S. typhi*, and *S. pyogens*, followed by methanolic extract showing potent activity against *P. aeruginosa*. This study also suggested that acetone and aqueous of *P. kurroa* possess moderate antibacterial active against *S. aureus*, *K. pneumoniae*, *B. cereus*, and *S. pyogens*, and therefore concluded that ethanolic and methanolic extracts of *P. kurroa* rhizomes comprise of compounds that can be used for development of novel broad spectrum antibacterial formulation (Kumar et al. 2010).

Surendra and Naresh studied the antimicrobial activity of chloroform, methanol, and aqueous extract of PK rhizome against bacterial and fungal strain using cup–plate method and ciprofloxacin and Fluconazole were used as standards. The results demonstrated that the methanolic extract showed significant antibacterial activity comparable to ciprofloxacin and aqueous extract showed potent antifungal activity as comparable to fluconazole hence concluded that *P. kurroa* rhizome extract possess significant antimicrobial activity (Sharma and Kumar 2012).

P. kurroa ethanolic extract was authenticated for its antimicrobial activity via agar well diffusion model. PK was found active against *B subtilis* and *P. aeruginosa* with minimum inhibitory concentration (MIC) values ranging from 65 to 260 mg / mL (Usman et al. 2012).

Diksha et al. evaluated antimicrobial activity of endophytes isolated from PK against human pathogens *S. typhimurium* (MTCC98), *S. aureus* (MTCC 96), *E. coli* (MTCC 1697), and *P. aeruginosa* (MTCC741). The results of the study concluded that MB-05 and MB-03 possess potent activity against *P. aeruginosa* whereas MB-09 and MB-15 showed potent activity against *S. typhimurium* and *S. aureus*. On the basis of antimicrobial potential, methanolic and chloroform extract of MB-05 were subject to HPLC analysis for the active metabolite identification (Raina et al. 2018).

A study was carried out to study antimicrobial activity of *P. kurroa* Benth rhizomes. Antimicrobial effect of the methanolic and aqueous extract was authenticated against *Micrococcus luteus*, *P. aeruginosa*, *B. subtilis*, *E. coli*, and *Staphylococcus aureus* bacterial strains. From the study, it was concluded that the extracts possess the significant antimicrobial activity but methanolic extract was found more potent against *S. aureus* and *P. aeruginosa*, which proved its traditional use in skin treatment, GIT infection, diarrhea, and urinary tract infection (UTI). Further, the iridoids, picroside I, and kutkoside were estimated using HPLC which was found to be 3.66 ± 0.11 and 4.44 ± 0.02 respectively (Rathee et al. 2016).

13.3.7 Antimalarial Effect of *P. kurroa*

Malaria, caused by *Plasmodium* parasites, a single-celled microorganism, which is transmitted from person to person through infected female *Anopheles* mosquitoes called "malarial vectors." Symptoms usually develop after 10–15 days after mosquito bite (World Health Organization 2016).

An in vivo study was carried out by Banyal et al. to evaluate the antimalarial effect of ethanolic extract of *P. kurroa* roots and leaves against *Plasmodium berghei* for 4 days. From the study it was found that after day 4, the ethanolic extract of PK significantly inhibited the malarial parasite and parasitemia. Root extract of PK showed potent activity as compared to leaves (Banyal et al. 2014).

Saba Irshad et al. evaluated the in vitro antimalarial activity of *Artemisia absinthium*, *P. kurroa*, and *Caesalpinia bonducella* at a dose of 2 mg/mL against *Plasmodium falciparum*. Maceration and percolation extraction procedures were used for the preparation of different extracts from different parts of these plants. Cold alcoholic, hot alcoholic, and aqueous extracts of PK at a dose of 2 mg/mL significantly inhibit the growth of *P. falciparum* viz. 100%, 90%, and 34%, respectively. Cold alcoholic, hot alcoholic, and aqueous extract of *Caesalpinia bonducella* at the same dose showed 56%, 70%, and 65% growth inhibition *P. falciparum*, respectively. Similarly, Cold alcoholic, hot alcoholic, and aqueous extract of *Artemisia absinthium* showed 55%, 21%, and 35% inhibition, respectively, at the same concentration. The study was concluded that among these plants PK possess good

antimalarial activity and also proved its traditional uses as antimalarial drug (Irshad et al. 2011).

13.3.8 Antiulcer Effect of *P. kurroa*

An ulcer is an eruption on stomach or small intestine lining caused by sloughing out of inflamed necrotic tissues. The causes for ulcers in stomach include *Helicobacter pylori* (*H. pylori*) infection and prolong use of nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin, ibuprofen, or naproxen. Sometimes a body increases its acid production due to unknown leads to stomach and intestinal ulcers which is commonly known as Zollinger–Ellison syndrome. Burning sensations or pain between chest and belly button are some common symptoms of this disease (Shiotani and Graham 2002). Debashish et al. investigated the antiulcer activity of PK20 mg/kg against acute stomach ulceration induced by indomethacin male Swiss albino mice and evaluated its potential to balance oxidative stress, prostaglandin (PGE_2) levels and EGF during the study. The methanolic extract of PK resulted in reduction of ulcer indices by 45.1% as compared by the standard drug Omeprazole (76.3%). Furthermore, extract reduces protein carbonyl (37.7%) and thiobarbituric acid reactive substances (TBARS) (32.7%), levels, and elevated mucosal PGE2 (21.4%), mucin (42.2%), cyclooxygenase-1 and 2 (COX-1 and -2) expressions (26.9 and 18.5%), epidermal growth factor (EGF) (149.0%), and vascular endothelial growth factor (VEGF) (56.9%) levels in the body. Hence, concluded that PK can be used an effective antiulcer agent, which can act by decreasing ROS-mediated stress and stimulate prostaglandin synthesis, mucin secretion promoting, and increasing cyclooxygenase enzymes and growth factors expression (Banerjee et al. 2008).

Arun et al. evaluated the antioxidant potential of PK at the concentration of 20 mg/kg for 10 days against indomethacin-induced acute gastric ulcers in rats. In gastric tissue, lipid peroxidized level in terms of TBARS and antioxidant enzymes, viz. SOD, catalase, and total tissue sulfhydryl group were studied during the investigation. The study concluded that the ethanolic extract of PK significantly enhanced the healing process in indomethacin-induced gastric ulcers. Furthermore, the extract also significantly increased the antioxidant enzymes. Therefore, ethanolic extract of PK rhizomes accelerate stomach wall healing in indomethacin-induced gastric ulceration probably by free radical scavenging action (Ray et al. 2002).

13.3.9 Analgesic Activity of *P. kurroa*

Analgesia, which results due to disruption in nervous system pathway, and the drugs which are used to get relief from pain are known as analgesic drugs or painkillers (Cregg et al. 2013). Neha et al. evaluated the analgesic and antipyretic activity of methanolic and hydroalcoholic extracts of *P. kurroa* rhizomes at a dose of 260 and 520 mg/kg using hot plate and yeast-induced pyrexia models. It was concluded from the results that the methanolic extract of *P. kurroa* at the dose of 260 and 520 mg/kg

possesses potent analgesic and antipyretic active as compared to hydroalcoholic extract which showed activity only on 520 mg/kg (Kaila and Dhir 2019).

Shid Rupali et al. evaluated the analgesic potential of PK roots at the concentration of 250 and 500 mg/kg for 7 days. The study was conducted using acetic acid-induced writhing and hot plate methods in albino mice. The results revealed that PK at 500 mg/kg showed similar analgesic effect as shown by standard drug pentazocine at ½ h. Furthermore, extract at 500 mg/kg significantly decreases the number of writhing that were induced by acetic acid, and concluded that *P. kurroa* possesses significant analgesic activity at the dose of 500 mg/kg (Shid Rupali et al. 2013).

13.3.10 Antiallergic Effect of *P. kurroa*

Allergies or allergic diseases are a group of conditions triggered by hypersensitivity of the immune system or allergen-induced unfavorable immune response typically to harmless substances from the environment, which typically could not be controlled completely by modern medicine (Kubo et al. 2017).

Baruah et al. investigate anti-anaphylactic and antiallergic activity of Picroliv (25 mg/kg). The results of the study showed that Picroliv significantly inhibits passive cutaneous anaphylaxis (82%) in mice and (50–85%) in rats. Further, it also protects mast cells from degranulation (60–80%) (Baruah et al. 1998).

13.3.11 Antiasthmatic Effect of *P. kurroa*

Asthma is a condition wherein the airway of the human respiratory system is constricted and narrowed. It occurs usually in reaction to a cause like cold, dust, allergen, exercise, or emotional stress affecting about 7% of total population, which approximately accounts for 300 million people worldwide. Asthma is associated with difficulty in breathing because of the inflammation of airways which occurs due to constriction of smooth muscle cells in bronchi (Ranjeeta et al. 2009).

Antiasthmatic activity of *P. kurroa* root ethanolic extract has been studied by in vitro and in vivo experimental model in guinea pigs by inducing histamine stimulated bronchoconstriction. A significant protection was observed with the extract (52.16%) which was comparable to that of salbutamol (65.83%). The molecular mechanism behind the muscle relaxant activity of the extract was also analyzed. The extract was found to be effective at a dose of 100 mg/mL against acetylcholine- and histamine-induced contraction. The result further revealed that antiasthmatic activity of the extract was due to presence of flavonoids and saponins (Sehgal et al. 2013).

13.3.12 Anti-Inflammatory Effect of *P. kurroa*

Inflammation is a defense mechanism wherein the human body responds to harmful stimuli like tissue injury or exposure to various allergy-causing substances (allergens). On the contrary, an uncontrolled response to inflammation is the reason for the vast number of diseases including allergies CVD dysfunctions, cancer, autoimmune disorders, etc. (Bagad et al. 2013; Mir et al. 2019, 2020).

It was reported that *P. kurroa* is an active anti-inflammatory drug due to the inhibition of edema at the rate of 29.8% (Kantibiswas et al. 1996). Similarly, application of *P. kurroa* rhizome extract was shown to considerably inhibit inflammation of joints against chemically induced inflammation. Owing to its anti-inflammatory activity it may be regard as a high-quality naturally occurring analgesic.

Pandey et al. also observed the anti-inflammatory activity of *P. kurroa* and confirmed that this activity was due to β-adrenergic blockade, suggesting that the plant extract was responsible for changes in biology of cell and it was also concluded that *P. kurroa* extract selectively have role in activation methods related to the membrane in inflammatory effect or cells which could be the cause of anti-inflammatory activity (Kumar et al. 2016).

13.3.13 Antioxidant Activity of *P. kurroa*

Antioxidants are the compounds that prevent or inhibit the oxidation and generally extend the life of the oxidizable matter (Kokate et al. 2003). Free radicals are produced in many biochemical processes and several diseases are allied to oxidative stress owing to free radical generation (Velavan et al. 2007). Antioxidant agents are radical scavengers that prevent the human body from various disorders (Kalaivani and Mathew 2010).

Antioxidant property of *P. kurroa* extract suggest its active role toward different oxidative stress–related diseases. Deshpande et al. reported that following the treatment with the extract of *P. kurroa*, the liver enzyme activities are reduced among the patients suffering from liver cirrhosis (Deshpande et al. 2015).

Rajkumar et al. reported the antioxidant effectiveness of extracts of *P. kurroa* by employing various methods, viz. ferric-reducing antioxidant activity, radical scavenging assays, and thiobarbituric acid assay for evaluating lipid peroxidation inhibition (Rajkumar et al. 2011a). Ray et al. established that the administration of PK rhizome ethanolic extract (20 mg/kg) promptly cured abdominal wall of gastric ulcerated rats (induced by indomethacin) (Ray et al. 2002). Krupashree et al. used diverse antioxidant testing methods to determine the antioxidant efficacy of the leaf fractions of PK. They found that the extract of *P. kurroa* demonstrated radical scavenging property and metal chelating activities (Krupashree et al. 2014). Sinha et al. evaluated the antioxidant properties of PK using in vitro methods and authenticated that *P. kurroa* aqueous extract has potent antioxidant activity. Furthermore, the addition of aqueous extract *P. kurroa* along with ethanol helped in the

re-establishment of antioxidant enzyme activity and suppression of lipid peroxidation (Sinha et al. 2011).

13.3.14 Anticonvulsant Activity of *P. kurroa*

Convulsion or epilepsy is the most common and foremost neurological disorder and around 5% of total population of the world acquires convulsion in their lifetime. Convulsions/epilepsy often causes transitory damage of perception, thereby leaving a person at the risk of physical harm (Kee et al. 2012).

Dilnawaz et al. studied the anticonvulsant activity of *P. kurroa* and ethanolic extract of its roots in mice using various inducing agents, viz. picrotoxin, pentylenetetrazole-induced seizures and electroshock-induced seizure. The convulsion latency and the number of animals protected from convulsions were noted and it was observed that the plant at a dose of 100 mg/kg exhibited substantial rise in clonic convulsion latency and also reduced the mortality (Pathan and Ambavade 2014).

13.3.15 Nephroprotective Effect of *P. kurroa*

The main functions of the kidneys include urine formation, water and electrolyte balance maintenance, as well as hormones and enzyme production. Kidneys also play an important role in the maintenance of endocrine, acid–base balance, and blood pressure. Nephrotoxicity is a renal dysfunction that develops in response toward exposure to external agents such as drugs and chemicals present in the environment (Priyadarsini et al. 2012; Sundararajan et al. 2014). An enormous number of chemicals that are commonly used nowadays are harmful to our kidneys (renal toxins). Administration of such chemicals/renal toxins into the body might trigger mechanical trauma to the kidneys and selectively interfere with some functions of the renal tubules.

Siddiqi et al. studied the effectiveness of *P. kurroa* against the toxicity induced by nimesulide. The in vitro study was performed on mice which were divided into four groups at National Institute of Health. One group was given only the plant extract while the other three groups were given a potential nephrotoxic drug, nimesulide, to induce nephrotoxicity for 3 days at a dose of 750 mg/kg. The serum urea and creatinine levels were measured by performing biochemical analysis of kidney. The results showed that out of total 20 mice, only 1 mouse could not survive while 19 mice of nimesulide group survived. The nimesulide group exhibited mean serum urea of 60 mg/dl, which reduced to 23 and 25 mg/dL with two doses of the plant extract. In the other group, mean creatinine level observed was 0.55 mg/dL, which was reduced to 0.21 and 0.19 mg/dL with two doses of the plant extract (Siddiqi et al. 2015).

Yamgar et al. studied nephrocurative and nephroprotective activity of the extract of *P. kurroa* rhizome (ethanolic extract) in mice against toxicity induced by cisplatin, through the evaluation of the levels of urea in blood and creatinine levels in serum.

On treatment with the ethanolic extract of the PK rhizome, the high levels of urea in blood and creatinine levels in serum were significantly reduced at a dose of 600 mg/kg. An Ayurvedic preparation, Arogyawardhini, containing PK as a basic constituent was also reviewed for the nephroprotective and nephrocurative actions against nephrotoxicity induced by cisplatin. This preparation was established to have better results in comparison to the rhizomic extract (Surekha et al. 2010).

13.4 Conclusion

From the above discussion it can be concluded that *P. kurroa* is valuable plant with range of ethnomedicinal and pharmacological significance. Due to the overexploitation of this plant it has been placed in list of endangered species by International Union for Conservation of Nature (IUCN). Therefore, the plant has a desperate need to be conserved. Varied pharmacological activities and presence of many bioactive compounds have been confirmed by studies, though many of them are yet to be quantified. The phytoconstituents and its biological activities reviewed in this study can help researchers to investigate this plant to further extent. Its utilization in different other diseases as well as its toxicity can be tested. Results have been based mostly on in vitro bioassay, but in vivo study employing humans is also required. Consequently, clinical trials should form a standard for safe therapeutic applications of this species.

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Lady's Purse (*Capsella bursa-pastoris* L.): Current Perspective on Its Ethnopharmacological, Therapeutic Potential, and Phytochemistry

14

Mohd Akbar Dar, Prince Ahad, Mubashir H. Masoodi, Showkat Rasool Mir, and Seema Akbar

Abstract

Capsella bursa-pastoris L. is widely found in countries such as Cyprus, Europe, Saudi Arabia, Turkey, Pakistan, India, Iraq, Iran, China, Azerbaijan, and in ethnomedical records of many other Asian countries. *C. bursa-pastoris* (L.) Medic—a traditional herb belongs to genus *Capsella*. Animal model-based preclinical studies have provided important comprehensive scientific data of its phytochemistry and phytopharmacology besides its various important uses. The main focus of this chapter aims to provide a detailed information about the traditional uses, scientific evidence-based pharmacological actions, and phytoconstituents from *C. bursa-pastoris* (L.) Medic based on the data available from the past 40 years. The data available shows that the plant's crude extracts and some phytoconstituents have anti-inflammatory, smooth muscles contraction, infertility, antimicrobial, hepatoprotective, cardiovascular, anticancer, sedative, antioxidant, acetylcholinesterase inhibition potential. The data also showed that *C. bursa-pastoris* (L.) has a good nutritional value due to the presence of plethora

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of phytoconstituents which include flavonoids, phytosterols, phenolics, etc. Other than immense pharmacological potential, *C. bursa-pastoris* is a rich source of nutrients also. The available scientific data on ethnopharmacology, phytochemistry, and pharmacological actions of *C. bursa-pastoris* suggest that this plant can be a promising target for discovery and development of novel drugs for treating wide range of human ailments due to the safe and effective nature of *C. bursa-pastoris.* More scientific studies need to be carried out on this plant because different traditional uses and phytoconstituents.

Keywords

Ethnopharmacology · Phytochemistry · Pharmacological actions · Phytosterols · Phenolics · Flavonoids · Anti-inflammatory · *C. bursa-pastoris*

14.1 Introduction

Capsella bursa-pastoris belongs to mustard family Brassicaceae and is a small annual or biennial, erect, glabrous, or hairy with simple or branched hairs and ruderal flowering herb which can attain height up to 0.5 m (1.6 ft). It is indigenous to Asia Minor and eastern Europe but in various parts of the world is also considered as a common weed, mostly in colder climates (Aksoy et al. 1998), including British Isles, where it is considered as an archaeophyte, Cyprus, Europe, Saudi Arabia, Turkey, China, and North America (Preston et al. 2004), but also in the Mediterranean and North Africa (Al-Douri and Al-Essa 2010; Al-Snafi 2015; Alizadeh et al. 2012). *C. bursa-pastoris* is known by several common and vernacular names like Shepherd's Sprout, Shepherd's Bag, Shepherd's Scrip, Lady's Purse, Rattle Pouches, Witches' Pouches, Case-weed, Pick-Purse, Pick Pocket, Blind weed, Poor Man's Parmacettie, Sanguinary, Pepper-and-Salt, Mother's Heart and Clappede pouch in English; *Bourse de Pasteur* in French; *Kess el Raee*, *Madakat el Raee*, *Gezdan el Raee*, *Karmala*, *Sharabat el Raee* in Arabic; *Hirtentasche* in German (Grieve 1980).

14.1.1 Scientific Classification

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Brassicales
Family: Brassicaceae
Genus: *Capsella*
Species: *bursa-pastoris*

14.1.2 Morphology

C. bursa-pastoris L. is an erect, annual, small herb. It possesses stems simple or branched from the base, 3-(10–40)-103 cm high, pale green to straw-colored, angled and sparsely hairy, glabrous or striate, hairs branched or simple. Stem leaves alternate, a rosette forming by basal leaves. Leaves are narrowed into a stalk and oblanceolate with a large terminal lobe and are varying from very deeply pinnatifid to entire (Holm et al. 1977).

Stem with acute basal auricles and variable shaped leaves. Flowers have pink or greenish calyx with white corolla, obovate petals 2–2.2 mm long, four in number and are in long, terminal racemes; the rachis and the ripening of seeds cause pedicel to elongated-along axis. Petals are up to two times in length as the hairy sepals. A two-valved silicula which is triangular-obcordate, emarginate above, on a spreading stalk 5–20 mm long and 3.6 and 8.8 mm in width and 5–9.2 mm long, centrally replum separated fruit. At the apex of the two valves, the fruit is notched, the tiny seeds fixed with the thin, membranous, elliptical septum after fruit falls at maturity and are yellowish-brown or dark-reddish, oblong and flattened, with three equally divided parts by two longitudinal grooves and are minutely roughened. There are up to 28 seeds per capsule. Between 0.139 and 0.164 mg, with a mean 0.150 mg ($n = 60$, SE = 0.004) is the dry weight of seeds. Taproot which often forks after about 10 cm and root system is constituted by few secondary roots (Holm et al. 1977).

There is extreme difference in the leaf form, and size of fruit in species worldwide, but *C. bursa-pastoris* with its long, terminal racemose inflorescences; its triangular seedpods which are at right angle to the stem and are flattened; its toothed leaves of the rosette, and its small white flowers that are its distinguishing features (Holm et al. 1977).

Based on morphological criteria, worldly different numbers of biotypes of *C. bursa-pastoris* in the field have recognized by various authors (Almquist 1907, 1926; Hameister 2009; Neuffer 1989; Shull 1909). The variation in phenotypic is the probable reason; annual weeds of cultivated land is the most common feature (Kay 1994). There are four biotypes according to leaf shape, as per Shull (1909) and Neuffer (1989), are as follows: A (simplex), B (rhomboidea), C (heteris), and D (tenuis); and all these have been reported from Britain (Aksoy 1996).

14.1.3 Distribution (Geographical and Altitudinal)

Europe and west Asia appears to be the center of distribution of genus *Capsella*. *C. bursa-pastoris* is richly distributed over British Isles but is less distributed toward north.

C. bursa-pastoris is widespread originated from Europe, and richly distributed throughout Asia, America, Australasia, and African countries (Holm et al. 1979). It is perceived at the latitude of 65°N in Iceland and to 71°N in Norway. It occurs in the

cooler highlands at a latitude of 4°N in Colombia and on the equator in Kenya at an elevation between 1600 and 2300 m (Aksoy et al. 1998).

The altitudinal variation of *C. bursa-pastoris* in England, which in North Yorkshire range from sea level to 366 m, and the variation in Durham to 466 m, and it has an altitudinal range from sea level to 381 m near Dublin in Ireland (Alt. Range Brit. Pl.). In Scotland, it is found at an elevation of 900 m (Mukherjee et al. 1984); therefore, in the British Isles, it occurs at an altitude from sea level to 900 m, and is also highly prevalent in plane areas.

C. bursa-pastoris occurs at an altitude of 2000 m from sea level in Turkey (Davis 1965); from sea level to 2700 m in Italy (Fenaroli 1932); in northern France-Pyrenees it has an altitude of about 1850 m; to 2091 m in Scandinavia (Neuffer 1990); and approximately 3000 m in the Alps (Fenaroli 1932). It is also found in northwest Himalaya at an elevation of almost 3000-–5900 m (Mani 1978).

14.1.4 Habitat

C. bursa-pastoris is found in warm temperature subtropical zones (dry-summer steppe as well as in dry summer Mediterranean climates with humid winters). They are found in cool temperate zones (such as oceanic, suboceanic, subcontinental, and humid steppe climates). *C. bursa-pastoris* is reported from the Nile Valley having an intermediate May temperature of ~27 °C and receives an average of 20 mm precipitation throughout the spring. It survives temperatures as low as 12 °C in an overwintering rosette in Germany. It is mainly found in the temperate zones than that of the tropic zones; if found in the tropics or subtropics, at higher elevations it is typically bountiful (Holm et al. 1977). Primarily *C. bursa-pastoris* is a species of uniform or mildly sloping land *C. bursa-pastoris* is richly present at south-facing slopes (Grime et al. 2014). *C. bursa-pastoris* is both rural and urban land species on especially cultivated land; it occurs notably as a garden weed and as a vegetable crop weed, in bare patches, and on path sides in damp to dry grasslands. It was reported as a winter annual on rock outcrops (Grime et al. 2014).

Destruction caused by wind or by solar radiations has not been prominent. The species has not been reported from persistent wet conditions, but it has been reported from some arid areas in some parts of its range, like the Isthmic Desert in Egypt (Hassib 1951).

C. bursa-pastoris is found predominantly on soils varying from clay to sandy loam and in the pH range of 5.0–8.0. Soil analysis from sites supporting *C. bursa-pastoris* gave a range for total nitrogen from 0.10 to 0.43%. Phosphorus ranged from 3.8 to 31.7 mg 100 g^{-1} and exchangeable potassium, magnesium, and calcium, extracted with M ammonium acetate (pH 9.0), ranged from 4.3 to 32.5 mg 100 g^{-1}, 178–1978 mg 100 g^{-1}, and 4–12 mg 100^{-1}, respectively. Soil depths ranged from 14 to about 40 cm (Aksoy 1996).

14.1.5 Traditional Uses

Traditionally *C. bursa-pastoris* is a commonly used herb for many purposes. This herb is used commonly for domestic remedies for various ailments, especially for the treatment of both external and internal bleeding, diarrhea, etc. (Grieve 1984; Foster and Duke 1990). For many centuries, the plant was used by Chinese and Japanese due to its various medicinal uses like to stop bleeding of wounds, increasing urine output, and for lowering the elevated body temperature (Kuroda and Takagi 1968).

The whole plant was used for the treatment of swelling caused due to some disorder in kidneys, painful urination, boils and piles, heavy menstruation in women, presence of chyle in urine, and in treating hypertension also. Koreans eat the root of C. *bursa pastoris* and also use it as medication for treating hypertension and edema (Song et al. 2007); its roots and leaves are utilized as raw or cooked herbs, while its growing roots and leaves are consumed and in some countries it is eaten raw or cooked (Zennie and Ogzewalla 1977; Kweon et al. 1996). The tea prepared from *C. bursa-pastoris* was used for different activities depending upon the part or form of the plant used. The tea prepared from the whole plant, which has antiscorbutic, astringent, diuretic, antihypertensive, stimulant, vasodilator and vulnerary properties; while the dried herb tea of this plant is used for controlling hemorrhages caused in different parts of the body like stomach, lungs, uterus, and mostly for kidneys. *C. bursa-pastoris* has been ranked on the seventh position among the 250 potent antifertility plant lists in China. The herb has been used during childbirth traditionally because of its proven uterine-contracting properties. For the treatment of nose bleeding and renal calculus, fresh parts of plant are used which makes this plant as a part of homeopathy (Grieve 1984; Him-Che 1985; Lust 1983). According to Wichtl, *C. bursa-pastoris* has a current use as astringent in traditional medicine. It is employed for preventing or arresting hemorrhage, more specifically to treat dysmenorrhea in European traditional medicine (Bisset 1994a, b). In Tibetan medicine, *C. bursa-pastoris* is practiced for the treatment of various disorders like kidneys, lungs, and nerve disorders *C. bursa-pastoris* is also used as an antiemetic and diuretic. C. *bursa pastoris* also has an importance in traditional Indian medicine, as it used for the treatment of hemorrhages from renal and genitourinary tract, menorrhagia, as diuretic and for treating diarrhea and dysentery (Khare 2007).

The plant in many traditions is used as folk remedy for cancer, as it has been proven to contain fumaric acid which shows reduced growth and viability of Ehrlich tumor in mice (Duke and Ayensu 1985). The therapeutic guide to herbal medicine in the German Commission E Monographs approve *C. bursa-pastoris* for treatment of nose bleeds, premenstrual syndrome, wounds, and burns (Chiej 1984).

Steinmetz (1954) has inferred that an infusion of *C. bursa-pastoris* is diuretic, an astringent, and has a cooling effect as well. Hence, it is useful in case of all kinds of blood and bladder problems which may include diarrhea with sharp and bloody stools, profuse menses, dropsy, piles, and also the diseases of bladder, spitting of blood. Extractum *C. bursa-pastoris* liquidum is employed as an alternate for ergot of rye to arrest bleeding from lungs, stomach, uterus, and kidneys. Steinmetz has marked the substantial hemostatic action of the fungi *Cystopus candidus* and

Peronospora grisea, which grow on the plant and produce the odor of trimethylamine (Steinmetz 1954). Wichtl stated that the previous common use of *C. bursa-pastoris* as a substitute for ergot in uterine hemorrhaging, and its continual application in folk medicine to treat dysmenorrhea (Bisset 1994a, b). Ergot is a stronger hemostyptic agent than *C. bursa-pastoris*, but Van Hellemont mentions that both ergot and *C. bursa-pastoris* in the treatment of menorrhagia and metrorrhagia showed beneficial effects (Van Hellemont 1988) (Figs. 14.1 and 14.2).

14.2 Pharmacology Report

The wide range of biological activities and pharmacological spectrum of medicinal herbs attract an immense interest in their health benefits. These herbs possess these unique activities due to the presence of different phytoconstituents. The various reported pharmacological activities of *C. bursa-pastoris* are as follows.

14.2.1 Antimicrobial Activity

Benzene extract of *C. bursa-pastoris* showed a significant antibacterial action. On the other hand, the broader antimicrobial spectra of *C. bursa-pastoris* may be due to presence of alkaloids and flavonoids (El-Abyad et al. 1990). Hasan et al. evaluated the antibacterial potential of this plant (ethanol and aqueous extracts) against eight different species of bacteria, including both gram positive as well as gram negative, namely, *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *proteus vulgaris*, *Serratia marcescens*, *A. baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. The results revealed that only gram-negative bacteria showed susceptibility toward the extracts. Furthermore, hot aqueous extract showed stronger potency than ethanol extract by using disc diffusion. Restricted growth of gram-negative pathogens at the concentration of 2000–3000 μg/mL by aqueous extract. *C. bursa-pastoris* ethanolic extract showed activity against *P. aeruginosa* and *K. pneumoniae* (Hasan et al. 2013). In another study, ethanol extract of *C. bursa-pastoris* exhibited significant antibacterial activity against six pathogens (*Enterococcus faecalis*, *Streptococcus mutans*, *S. sanguis*, *S. aureus*, *A. viscosus*, and *Escherichia coli* also pathogens do not develop any kind of resistance against the extract (Soleimanpour et al. 2013, 2015). Revealed by results of another study, inhibition of vancomycin-resistant pathogenic bacteria *enterococci* and *Bacillus anthracis* by a sulforaphane isolated from *C. bursa-pastoris* in a solution form at minimal inhibitory concentration of 250 μg/mL and 1000 μg/mL respectively (Choi et al. 2014). Shepherin-I and shepherin-II were isolated from the roots of *C. bursa-pastoris* are two important antimicrobial peptides containing 28 and 38 amino acids respectively, with gly–gly–his chains having antifungal activity, also possessing antimicrobial potential on gram-negative bacteria (Park et al. 2000). In one more study screening of methanol, extracts of *C. bursa-pastoris* from methanol/water and dichloromethane against various gram-positive bacteria, which include

Fig. 14.1 *C. bursa-pastoris*

Staphylococcus aureus, *S. epidermidis*, *Micrococcus luteus*, *Enterococcus faecalis*, and *Bacillus cereus*; and four gram-negative bacteria, including *Proteus mirabilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium* for their antibacterial potential and greater antibacterial inhibition showed by methanol

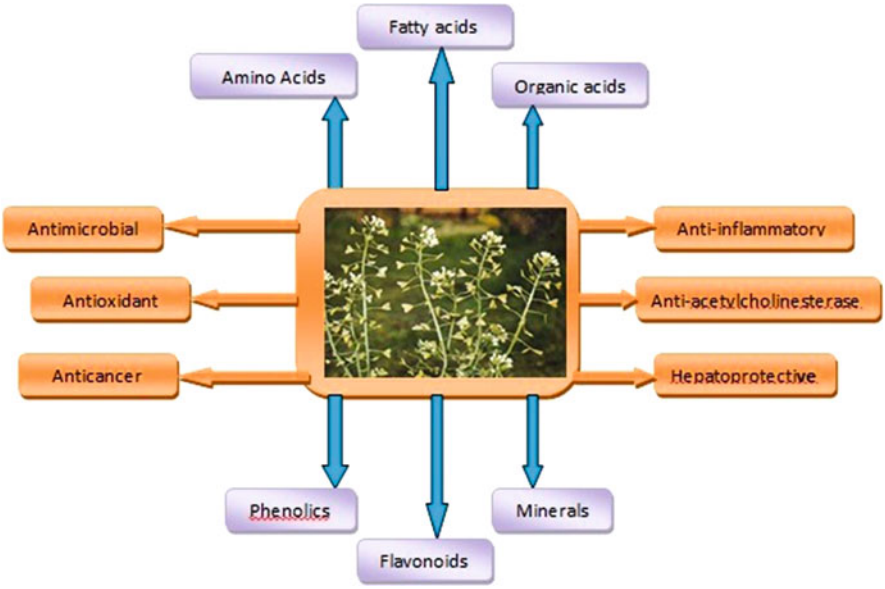


Fig. 14.2 Various reported pharmacological properties of *C. bursa-pastoris*

Table 14.1 Minimal inhibitory concentration (MIC) of *C. bursa pastoris* (L.) Medik. extracts tested against Gram-positive and Gram-negative bacteria

Organism tested	MeOH	MeOH/H_2O	Dichloromethane
Gram positive			
Staphylococcus aureus	63.00	32.00	>125.00
Staphylococcus epidermidis	32.00	32.00	>125.00
Micrococcus luteus	32.00	32.00	>125.00
Enterococcus faecalis	63.00	32.00	>125.00
Bacillus cereus	63.00	32.00	>125.00
Gram negative			
Proteus mirabilis	>125.00	>125.00	>125.00
Escherichia coli	>125.00	>125.00	>125.00
Pseudomonas aeruginosa	>125.00	>125.00	>125.00
Salmonella typhimurium	>125.00	>125.00	>125.00

extract than other two extracts (Grosso et al. 2011). The methanol and methanol/aqueous extracts showed minimum inhibitory concentrations (MICs) lower than dichloromethane (DCM) extract. Moreover, it is more active toward gram-positive bacteria than gram-negative ones (Table 14.1). The methanol/water extract was more effective in a general way, with MICs less than 32 mg/mL against all gram-positive bacteria, whereas methanol extract was found effective only against *S. epidermidis* and *M. luteus*. Since some patients having weak immune system are more vulnerable

to these two microorganisms. Extracts possessing activity against these bacteria are of great value. MICs observed for methanol/aqueous extract were lower than those observed for methanol extract against *S. aureus*, *E. faecalis*, and *B. cereus*. The potent activity against these pathogenic microorganisms is also of great importance, as they may cause endocarditis and urinary tract infections (UTIs) (*E. faecalis*) (Prescott et al. 1996).

14.2.2 Anticancer Activity

Fumaric acid isolated from *C. bursa-pastoris* significantly reduced the growth of Ehrlich, L1210, and MH134 mouse tumor cells in culture at concentration of 0.3–1.2 mg/mL (CP., 2007; Kuroda and Akao 1981; Khare 2008). Another study revealed the tumor inhibition of 2.9%, 29.5%, and 42.9% by ethanolic, methanolic, and aqueous extracts of *C. bursa-pastoris*, respectively (Yildirim et al. 2013). Concentration-dependent inhibition of cell growth by methanol extract of *C. bursa-pastoris* on HSC-2 human oral cancer cell apoptosis was evaluated in another study (Lee et al. 2013).

14.2.3 Anti-Inflammatory Activity

Anti-inflammatory potential of *C. bursa-pastoris* was proved by a study in which dextran- and carrageenan-induced rat paw edema was successfully treated by extracts from this plant. Histamine-induced capillary permeability in guinea pig was effectively decreased by extract of *C. bursa-pastoris.* Sulforaphane-containing solution (SCS) isolated from *C. bursa-pastoris* studied to have anti-inflammatory potential besides in lipopolysaccharide-stimulated RAW 264.7 murine macrophages causes decreases in quantity the of nitric oxide (NO) production, also the production of prostaglandin (PGE2) and cytokines (interleukin 1β [IL-1β], IL-6, and IL-10) (Choi et al. 2014; Hur et al. 2013).

In another study, anti-inflammatory activity of 14 compounds, namely, 10-methylsulphinyl-decanenitrile, methyl-1-thio-β-D-glucopyranosyl disulfide, 11-methylsulphinyl-decanenitrile, 1-O-(lauroyl) glycerol, phytene-1, 2-diol, (3S,5R,6S,7E)-5,6-epoxy-3-hydroxy-7-megastigmen-9-one, β-sitosterol, loliolide, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone, 1-feruloyl-β-D-glucopyranoside, pinoresinol-4′-O-β-D-glucopyranoside, quercetin-3-O-β-D-glucopyranoside, luteolin, and luteolin 6-C-β-glucopyranoside isolated from *C. bursa-pastoris* was studied by measuring the production of nitric oxide (NO) levels in microglia BV-2 cells (lipopolysaccharide (LPS) activated). The results revealed that luteolin strongly inhibited levels of NO ($IC_{50} = 9.70$ μM) better than NG-mono-methyl-L-arginine (L-NMMA) positive control (17.40 μM). Methyl-1-thio-β-D-glucopyranosyl disulfide and 1-O-(lauroyl) glycerol, moderately inhibits the production of NO (44.10 μM and 32.60 μM, respectively), but less significant effects was observed in other compounds (Table 14.2) (Cha et al. 2018). In another

Table 14.2 Effect of compounds 1–14 on NO production in LPS-activated BV-2 cells

Compound	IC_{50} (mM)	Cell viability (%)
28	44.10	118.28 ± 6.54
29	75.23	136.44 ± 5.13
30	144.64	117.91 ± 8.44
31	32.60	136.20 ± 11.20
32	153.71	152.92 ± 3.50
33	167.24	117.44 ± 2.83
34	>500	114.70 ± 8.48
35	77.12	119.36 ± 6.1
36	259.50	135.42 ± 10.68
37	63.55	112.15 ± 2.94
38	266.61	107.41 ± 2.63
39	9.70	137.66 ± 3.11
40	77.17	119.36 ± 6.13
41	146.69	120.36 ± 3.88
L-NMMA	17.40	110.21 ± 4.56

study, significant anti-inflammatory effects were observed by the ethyl acetate extract used at different doses (100, 200, and 300 mg/kg) after different time intervals, viz., 10 h ($p < 0.01$), 5 h ($p < 0.01$), and 3 h ($p < 0.01$), respectively, in carrageenan-induced paw edema experimental rats. Also the same extract in one more study showed significant anti-inflammatory action at the doses 200 and 300 mg/kg after 4 h ($p < 0.01$) and 2 h ($p < 0.01$), respectively on the egg albumin-induced inflammation experimental rats (Lan and Qing-Hu 2017). These anti-inflammatory effects may be attributed by flavonoids and alkaloids in *C. bursa-pastoris* (Bai et al. 2013; Meng et al. 2003; Morimoto et al. 1988).

14.2.4 Effects on Smooth Muscles

After *C. bursa-pastoris* extracts was evaluated for acetylcholinesterase inhibition, the results revealed that this plant is a moderate inhibitor of acetyl cholinesterase enzyme (Grosso et al. 2011). A stimulatory effect on small intestine of guinea pig by *C. bursa-pastoris* extracts was studied which was not affected by an anticholinergic drug atropine and diphenhydramine, but were inhibited by papaverine (Jurisson 1971). Also, *C. bursa-pastoris* extract induced very strong contraction on small intestines and uterus of guinea pigs due to *C. bursa-pastoris* extracts, which due to quaternary ammonium salt was isolated later from this extract (Khare 2008). Some isolated compounds from alcoholic extract of *C. bursa-pastoris* showed the contraction of rat uterus same as that of produced by oxytocin (Kuroda and Takagi 1968). Also, in another study, an infusion from *C. bursa-pastoris* caused a marked rise in uterine tone in isolated uterine of rabbit and guinea pig (Shipochliev 1981).

14.2.5 Infertility Effect

East (1955) carried out a study on infertility effect of dried and ground *C. bursa-pastoris*. The results revealed that there was 40% inhibition of ovulation which leads to male and female infertility when 20 and 40% of *C. bursa-pastoris* was incorporated in the diet of male and female mice (East 1955).

14.2.6 Antioxidant Activity

Antioxidant study was found in essential oils present in the *C. bursa-pastoris* aerial parts from Iran were obtained by steam distillation and phytochemical composition of oils were analyzed by GC-MS. The antioxidant potential of essential oil was examined by method of DPPH assay. EC_{50} obtained was 100.17 mg/mL of essential oil and for ascorbic acid and BHT it was 0.15 and 0.3 mg/mL. The results revealed that essential oil of from this plant doesn't possess a significant antioxidant property (Kamali et al. 2015a, b). Besides, flavonoids present in *C. bursa-pastoris* (methanolic and aqueous extracts) have a capacity to scavenge DPPH free radicals, peroxyl free radicals, hydroxyl free radicals, and hydrogen peroxide free radicals, hence antioxidant in nature as per study (Kubinova et al. 2013). Free radical scavenging nature of these extracts reveal that *C. bursa-pastoris* is having antioxidant potential (Grosso et al. 2011). In another antioxidant activity study, a concentration-dependent antioxidant potential was observed (Table 14.3), which follows the pattern with the Brassicaceae family plants (Orhan et al. 2009). *C. bursa-pastoris*-based methanol/water extract showed highly significant scavenging of $DPPH^{\bullet}$, $O_2^{\bullet-}$, and $^{\bullet}NO$, while methanol was significant for $LOO^{\bullet}$ scavenging.

Extracts from plants that significant scavenge $O_2^{\bullet-}$ and $^{\bullet}NO$ radicals are of immense importance, because of their neutralizing ability against other highly reactive free radicals such as peroxynitrite, etc. (Pacher et al. 2007).

14.2.7 Cardiovascular Effects

An increased myocardial blood flow was seen in dogs after the administration of extract of *C. bursa-pastoris* via the intra-arterial route, while as in rats a slight inhibition on ouabain-induced ventricular fibrillation was reported following an intraperitoneal injection of *C. bursa-pastoris* extract. *C. bursa-pastoris* showed

Table 14.3 Antioxidant and acetylcholinesterase inhibitory potential of extracts from *C. bursa-pastoris* (L.) Medik[a]

Assays	Methanol extract	Methanol:Aqueous extract
$DPPH^{\bullet}$	1041.49	420.96
$O_2^{\bullet-}$	538.03	167.60
$^{\bullet}NO$	0.2360	0.20
$LOO^{\bullet}$	0.46	906.02

[a]EC_{50} values (μg/mL) are expressed as mean of three assays

negative inotropic and chronotropic effects on guinea pig and rabbit hearts (Jurisson 1971). A decrease of permeability in the walls of blood vessel in white mice brought about by *C. bursa-pastoris* which may be due to hesperidin and rutin present in young leaves of this plant were also reported (Khare 2008).

14.2.8 Hepatoprotective Activity

Hepatoprotective effect of *C. bursa-pastoris* was studied on carbon tetrachloride–induced hepatotoxicity produced in rats. A total of 500 mg/kg dose body weight ($p < 0.05$) of extract of aerial parts of *C. bursa-pastoris* showed 26.9% and 31.7% decrease in serum glutamic oxaloacetic transaminase (SGOT) and bilirubin levels respectively (Alqasoumi et al. 2008). Also, Ma et al. (2016) reported the hepatoprotective activities of isolated compounds form ethyl acetate extract of *C. bursa-pastoris* against *d*-galactosamine-induced WB-F344 cell damage with the bicyclol as the positive control drug. The results revealed that 4′,7-dihydroxy-5-hydroxymethy-6,8-diprenylflavonoid (DHDF), chrysoeriol-7-O-β-D-glucopyranoside (CGP), and Sinensetin (SS) at 10 μM against bicyclol as standard exhibited significant hepatoprotective activities (Table 14.4) (Ma et al. 2016).

14.2.9 Sedative Effects

CNS-depressant action of *C. bursa-pastoris* was revealed by study potentiation of barbiturate-induced sleeping time in mice which confirms its sedative effect (Jurisson 1971).

14.2.10 Acetylcholinesterase Inhibitor Activity

A study was carried out on methanol and methanol/water extracts of aerial parts of *C. bursa-pastoris* for evaluating its acetylcholinesterase inhibitory activity which

Table 14.4 Hepatoprotective effects of selective compounds against *d*-galactosamine-induced toxicity in WB-F344 cells

Compound	Cell survival rate (% normal)	Inhibition (% control)
Normal	100.0 ± 7.3	–
Control	32.2 ± 2.1	–
Bicyclol	53.4 ± 6.5	31.3
DHDF	63.7 ± 8.2	46.5
CGP	49.9 ± 4.6	26.1
SS	51.9 ± 4.1	29.1

4′,7-Dihydroxy-5-hydroxymethy-6,8-diprenylflavonoid (DHDF), glucopyranoside (CGP) Sinensetin (SS)

was confirmed by their EC_{50} values (μg/mL) 909.44 for methanol extract, 3579.41 for methanol/water extract respectively (Grosso et al. 2011).

14.2.11 Effects on Psoriasis and Multiple Sclerosis

The valuable effect on multiple sclerosis and psoriasis due to inducing dendritic cells (type II) by fumarates (found abundantly in *C. bursa-pastoris*) were evaluated in mice. In vitro and in vivo studies showed IL-4-producing Th2 cells induced by dendritic cells (type II), are induced by fumarates from *C. bursa-pastoris*, and results in protection of mice from experimental autoimmune encephalomyelitis. The decrease in fumarate-induced glutathione (GSH) levels resulted in Type II DCs followed by increase in expression of hemoxygenase-1 (HO-1) and impairment in phosphorylation of STAT1. On cleavage of HO-1, the fragment of N-terminal from HO-1 interacts with IL-23p19 promoter via AP-1 and NF-κB sites in the nucleus (Ghoreschi et al. 2011).

14.3 Phytochemistry Report

The various phytoconstituents reported from *C. bursa-pastoris* are given in Table 14.13, and are as follows.

14.3.1 Phenolics and Flavonoids

Nine flavonoids include tricin, quercetin, quercetin-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside, kaempferol, kaempferol-7-O-α-L-rhamnopyranoside, quercetin-6-C-β-D-glucopyranoside, quercetin-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside, kaempferol-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside, and kaempferol-3-O-rutinoside were isolated from of *C. bursa-pastoris* whole plant extract (Kubinova et al. 2013; Song et al. 2007). Kaempferol-3-O-rutinoside, Quercetin-6-C-glucoside, quercetin-3-O-glucoside, quercetin, and kaempferol were also isolated from *C. bursa-pastoris* in methanol and methanol/water extracts (Grosso et al. 2011). The presence of phenolic moieties in both methanol and methanol/water extracts, representing about 65% and 51% of total determined phytochemical content is Kaempferol-3-O-rutinoside, respectively (Table 14.5). Capselloside was reported

Table 14.5 Flavonoids composition of *C. bursa-pastoris* (L.) Medik (mg/kg of dry plant)

Flavonoid	Methanol	Methanol/water
Quercetin-6-C-glucoside	793.90 ± 8.8	564.32 ± 8.09
Quercetin-3-O-glucoside	0426.26 ± 1.012314	1241.25 ± 37.61
Kaempferol-3-O-rutinoside	61 ± 11.59	2179.57 ± 67.68
Quercetin	16.36 ± 0.59	110.86 ± 15.69
Kaempferol	16.01 ± 0.12	130.41 ± 12.27

from *n*-butanol fraction of *C. bursa-pastoris* (Cha et al. 2018; Cha et al. 2017). Other phenolics glycosides reported from *C. bursa-pastoris* are 7S,8R, 8′R-(−)-lariciresinol-4,4′-*bis*-O-glucopyranoside (El Gamal et al. 1997), lariciresinol4-′-O-β-D-glucoside (Karioti et al. 2007), (+)-pinoresinol-β-D-glucoside (Kim et al. 2005), salidroside (Akita et al. 2006), 3-(4-β-D-glucopyranosyloxy-3,5-dimethoxy)-phenyl-2E-propanol (Greca et al. 1998), β-hydroxy-propiovanillone 3-O-β-D-glucopyranoside (Kim et al. 2010), and coniferin (Han et al. 2006). Two new flavonoids named 4′,7-dihydroxy-5-hydroxymethy-8-prenylflavonoid and 4′,7-dihydroxy-5-hydroxymethy-6,8-diprenylflavonoid were isolated from *C. bursa-pastoris* whole plant (Ma et al. 2016). Chrysoeriol-7-O-β-D-glucopyranoside, Acacetin-7-O-β-D-glucopyranoside (Zhang et al. 2005), licoflavonol (Kwon et al. 2010), icaritin (Gao et al. 2013), sinensetin (Jain and Zutshi 1973). In another study by Joon Min Cha (Cha et al. 2018), 14 compounds were isolated from *C. bursa-pastoris*, namely, methyl-1-thio-β-D-glucopyranosyl disulfide, 10-methylsulphinyl-decanenitrile, 11-methyl-sulphinylundecanenitrile, 1-O-(lauroyl) glycerol, phytene-1, 2-diol, loliolide, β-sitosterol, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone, quercetin-3-O-β-D-glucopyranoside, 1-feruloyl-β-D-glucopyranoside, (3S, 5R, 6S, 7E)-5, luteolin, 6-epoxy-3-hydroxy-7-megastigmen-9-one, pinoresinol-4′-O-β-D-glucopyranoside and luteolin 6-C-β-glucopyranoside.

14.3.2 Phytosterols

From dichloromethane extract of *C. bursa-pastoris* phytosterol compounds include ergosta-4,6,8,22-tetraen-3-one, stigmasterol, campesterol, cholesterol, β-sitosterol, cholest-5-en-3-one were reported, and also stigmasta-3,5-dien-7-one, lupeol, stigmasta-4-en-3-one were isolated besides. Some unidentified phytosterols (Grosso et al. 2011) and their detailed relative contents are shown in Table 14.6 (Grosso et al. 2011). The only sterol isolated β-sitosterol was the main compound; thus, the other compounds reported against it because its abundance was considered as 100% as shown in Table 14.6. Besides, isothiocyanate and sulforaphane were also isolated from *C. bursa-pastoris* (Choi et al. 2014).

Table 14.6 Relative abundance of phytosterol compounds identified in dichloromethane extracts of *C. bursa-pastoris* (L.) Medik by GC-ITMS analysis

Compound	Relative abundance (%)
Cholesterol	6.77 ± 1.46
Campesterol	38.12 ± 0.35
Stigmasterol	5.97 ± 0.06
β-Sitosterol	100.00 ± 0.00
Cholest-5-en-3-one	4.51 ± 0.23
Ergosta-4,6,8(14),22-tetraen-3-one	3.01 ± 0.02
Lupeol	2.33 ± 0.08
Stigmasta-3,5-dien-7-one	2.32 ± 0.34
Stigmasta-4-en-3-one	13.97 ± 0.23

14.3.3 Fatty Acids

Fatty acid constituents of oil derived from the seeds and roots of *C. bursa-pastoris* include different acids like azelaic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid, and 11-eikozenoic acid were reported. The content of acids was found to be different in oil from different parts of *C. bursa-pastoris*. On comparing the seed and root oils of *C. bursa-pastoris*, the results revealed that oils from seeds was having high content of unsaturated fatty acids (oleic acid, linoleic acid, and linolenic acid), whereas the oil from root was rich in palmitic acid (Ceyda 2007).

But it was reported that from dried plant of *C. bursa-pastoris* the free fatty acids were isolated include tetradecanoic acid (myristic acid), dodecanoic acid (lauric acid), pentadecanoic acid, (Z)-9-hexadecenoic acid (palmitoleic acid), (Z)-7-hexadecenoic acid, hexadecanoic acid (palmitic acid), heptadecanoic acid, 9,10-(Z)-methylenehexadecanoic acid, (Z)-9,12-octadecadienoic acid (linoleic acid), (Z)-9-octadecenoic acid (oleic acid), (Z)-6-octadecenoic acid, octadecanoic acid (stearic acid), and eicosanoic acid (arachidic acid) was isolated as methyl esters and their relative contents are shown in Table 14.7 (Grosso et al. 2011).

14.3.4 Organic Acids

In *C. bursa-pastoris* acidic extract six organic acids were recognized, in significant concentrations ranging from 8.02 to 95628.00 mg/kg (Table 14.8). Citric acid, malic acid, and quinic acid constituted 97% of the total content of organic acids (Grosso et al. 2011; Guil-Guerrero et al. 1999).

Table 14.7 Free fatty acids composition of *C. bursa-pastoris* (L.) Medik

Free fatty acid		Content (mg/kg of dry plant)
C12:0	Dodecanoic acid (lauric acid)	5.66 ± 1.17
C14:0	Tetradecanoic acid (myristic acid)	29.63 ± 5.79
C15:0	Pentadecanoic acid	18.05 ± 3.06
C16:1	(Z)-9-hexadecenoic acid (palmitoleic acid)	23.29 ± 0.49
C16:1	(Z)-7-hexadecenoic acid	22.97 ± 4.27
C16:0	Hexadecanoic acid (palmitic acid)	284.48 ± 41.06
C17:0	9,10-(Z)-methylene-hexadecanoic acid	17.59 ± 2.18
C17:0	Heptadecanoic acid	7.11 ± 1.60
C18:2	(Z)-9.12-octadecadienoic acid (linoleic acid)	20.09 ± 4.35
C18:1	(Z)-9-octadecenoic acid (oleic acid)	53.03 ± 9.99
C18:1	(Z)-6-octadecenoic acid	9.00 ± 0.08
C18:0	Octadecanoic acid (stearic acid)	53.20 ± 0.68
C20:0 Eicosanoic acid (arachidic acid)		2.52 ± 0.33

Table 14.8 Organic acid composition of *C. bursa-pastoris* (L.) Medik

Organic acid	Content (mg/kg of dry plant)
Oxalic	2416.98 ± 405.50
Citric	27408.80 ± 4161.68
Malic	68288.82 ± 11217.03
Quinic	95628.00 ± 15827.51
Shikimic	8.02 ± 1.15
Fumaric	3540.02 ± 546.01

14.3.5 Amino Acids

Threonine and isoleucine were outlined from methanolic extract of *C. bursa-pastoris* and glutamic acid, asparagine, and tryptophan were reported from methanolic–aqueous extract of *C. bursa-pastoris*. From these extracts, the main amino acids isolated were arginine and tyrosine, with arginine almost represents more than 50% and the tyrosine 30% of the total content of amino acid (Table 14.9) (Grosso et al. 2011). Shepherin-I and shepherin-II were isolated from the roots of *C. bursa-pastoris*, which are composed of peptides containing 28 and 38 amino acids respectively (Park et al. 2000).

14.3.6 Total Crude Fiber and Total Mineral Contents

Murat Tuncturk carried out the chemical analysis of *C. bursa-pastoris*, which revealed that *C. bursa-pastoris* was rich with some minerals. Total ash, nitrogen,

Table 14.9 Amino acids composition of *C. bursa-pastoris* (L.) Medik. (μg/kg of dry plant)

Amino acid	MeOH	MeOH/H_2O
Glutamic acid	–	Traces
Asparagine	–	3.77 ± 0.47
Serine	4.01 ± 0.43	1.39 ± 0.11
Threonine	4.93 ± 0.61	–
Glycine	12.23 ± 0.65	9.17 ± 0.63
Alanine	Traces	Traces
Valine	23.71 ± 1.32	11.15 ± 0.30
Proline	80.51 ± 5.33	36.10 ± 4.22
Arginine	1054.57 ± 44.11	1296.55 ± 77.89
Isoleucine	23.24 ± 2.10	–
Leucine	14.58 ± 0.72	7.42 ± 0.83
Tryptophan	–	2.51 ± 0.38
Phenylalanine	6.51 ± 0.55	174.83 ± 6.41
Cysteine	86.24 ± 3.30	149.09 ± 6.07
Ornitine	8.19 ± 0.75	3.31 ± 0.30
Lysine	Traces	12.49 ± 0.71
Histidine	6.05 ± 0.58	54.03 ± 3.87
Tyrosine	522.78 ± 45.88	796.97 ± 29.40

Table 14.10 Mean values of chemical composition values of *C. bursa-pastoris*

Parameters	Content
Dry matter (%)	18.72 ± 0.85
Total ash (%)	7.50 ± 0.70
N (%)	2.94 ± 0.08
Crude protein (%)	17.84 ± 0.56
pH	6.11 ± 0.18
Crude fiber (%)	24.30 ± 0.94

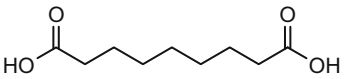
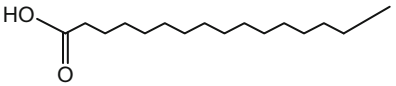
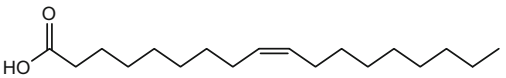
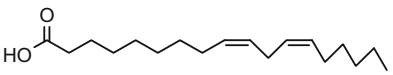
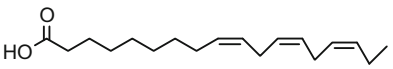
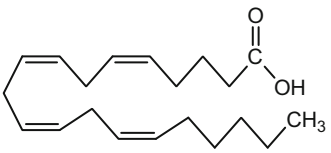
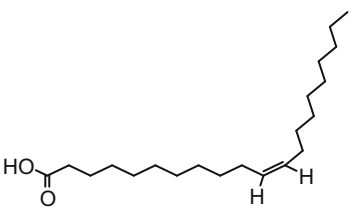
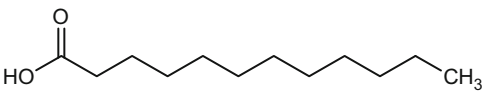
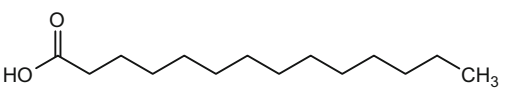
Table 14.11 Mean values of mineral compositions of *C. bursa-pastoris*

Minerals	Content
Na (g/kg)	0.44 ± 0.04
Mg (g/kg)	1.55 ± 0.13
K (g/kg)	19.23 ± 1.11
Ca (g/kg)	9.35 ± 0.09
P (g/kg)	2.40 ± 0.07
S (g/kg)	1.36 ± 0.04
Mn (mg/kg)	47.83 ± 2.02
Fe (mg/kg)	254.55 ± 9.34
Cu (mg/kg)	12.53 ± 0.51
Zn (mg/kg)	23.82 ± 0.61
Cr (mg/kg)	0.49 ± 0.08
Cd (mg/kg)	0.08 ± 0.01
Co (mg/kg)	1.26 ± 0.07
Pb (mg/kg)	0.06 ± 0.02

Table 14.12 Chemical composition of the essential oil of *C. bursa-pastoris*

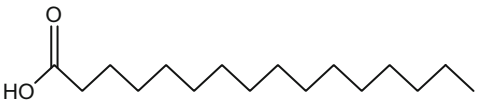
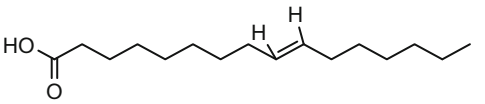
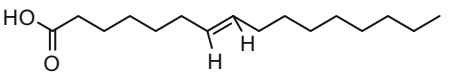
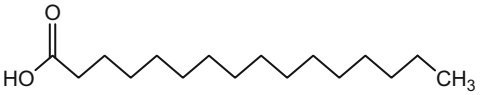
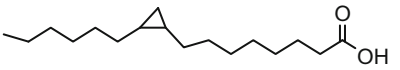
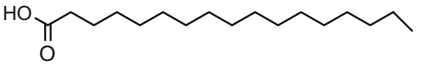
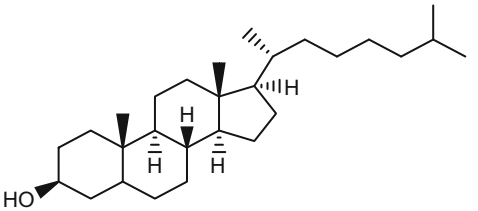
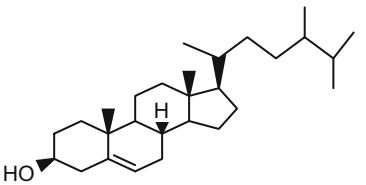
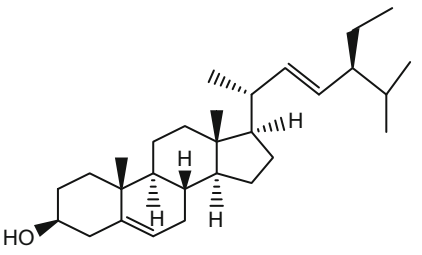
Compound	Area%
1,1-Dimethylcyclopentane	16.67
2,4-Dimethylpentane	2.27
Cyclohexane	8.46
3-Methylhexane	1.76
Trans-1,2-Dimethylcyclopentane	2.48
Toluene	3.05
3-MethylHeptane	2.74
Cis-1-ethyl-3-methylcyclopentane	1.26
Cis-1-ethyl-3-methylcyclopentane	1.45
Octane	5.56
2,4-dimethylhexane	10.36
p-Xylene	2.44
Allylisothiocyanate	4.92
Decane	7.03
Dodecane	3.20
Phytane	1.21
Ethyl linoleate	7.26
Palmitic acid	4.76
Nonacosane	1.32

Table 14.13 Chemical constituents reported from *Capsella bursa-pastoris*

Constituent	Structure
Azelaic acid (CEYDA)	
Palmitic acid (CEYDA)	
Stearic acid (CEYDA)	
Oleic acid (CEYDA)	
Linoleic acid (CEYDA)	
Linolenic acid (CEYDA)	
Arachidonic acid (CEYDA)	
11-Eicosenoic acid (CEYDA)	
Dodecanoic acid (lauric acid) (Grosso et al. 2011)	
Tetradecanoic acid (Grosso et al. 2011)	

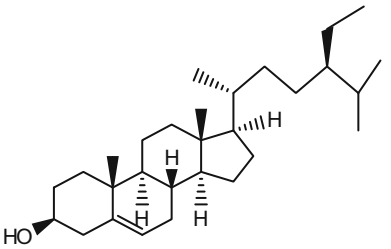
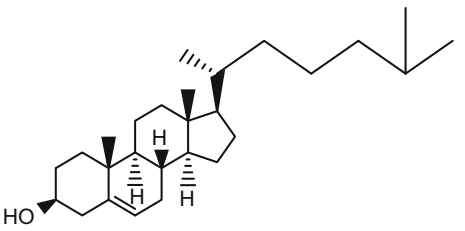
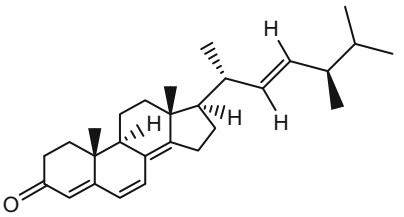
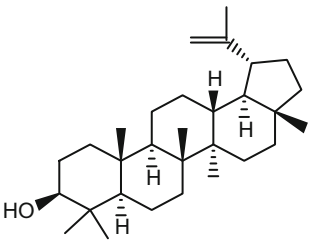
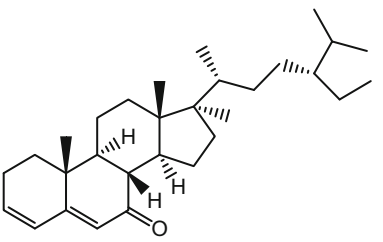
(continued)

Table 14.13 (continued)

Constituent	Structure
Pentadecanoic acid (Grosso et al. 2011)	
(Z)-9 hexadecenoic acid (Grosso et al. 2011)	
(Z)-7 hexadecenoic acid (Grosso et al. 2011)	
Hexadecanoic acid (Grosso et al. 2011)	
9,10-(Z)-Methylenehexadecanoic acid (Grosso et al. 2011)	
Heptadecanoic acid (Grosso et al. 2011)	
Cholesterol (CEYDA)	
Campesterol (CEYDA)	
Stigmasterol (CEYDA)	

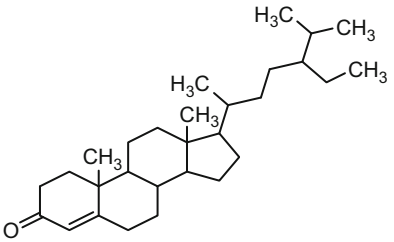
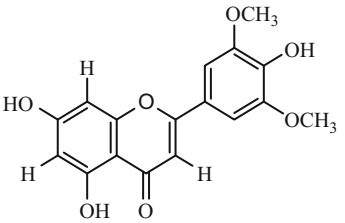
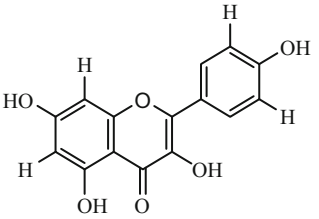
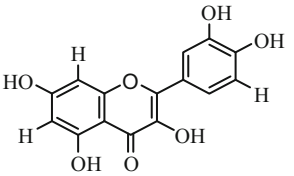
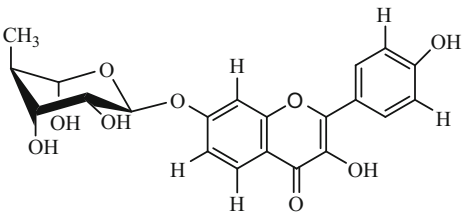
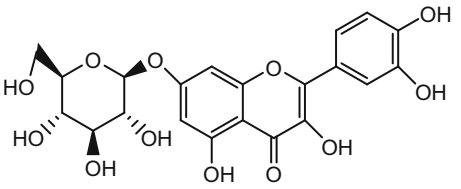
(continued)

Table 14.13 (continued)

Constituent	Structure
β-Sitosterol (CEYDA)	
Cholest-5-en-3-one (CEYDA)	
Ergosta-4,6,8(14),22-tetraen-3-one (CEYDA)	
Lupeol (CEYDA)	
Stigmasta-3,5-dien-7-one(CEYDA)	

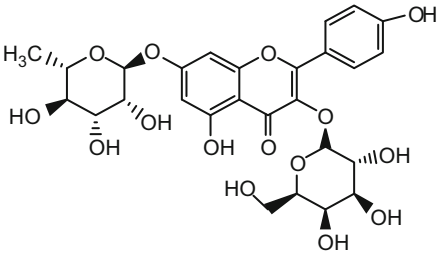
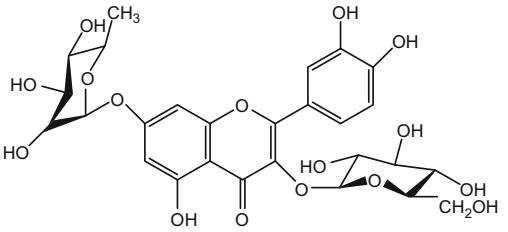
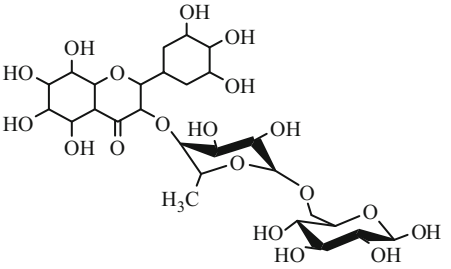
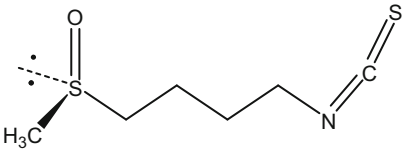
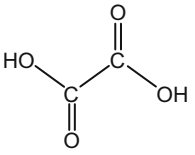
(continued)

Table 14.13 (continued)

Constituent	Structure
Stigmasta-4-en-3-one (CEYDA)	
Tricin (Song et al. 2007)	
Kaempferol (Kubinova et al. 2013; Song et al. 2007)	
Quercetin (Kubinova et al. 2013; Song et al. 2007)	
Kaempferol-7-O-α-L-rhamnopyranoside (Kubinova et al. 20133)	
Quercetin-6-C-β-D-glucopyranoside (Kubinova et al. 2013)	

(continued)

Table 14.13 (continued)

Constituent	Structure
Kaempferol-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside (Kubinova et al. 2013; Song et al. 2007)	
Quercetin-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside (Kubinova et al. 2013; Song et al. 2007)	
Kaempferol-3-O-rutinoside (Kubinova et al. 2013; Song et al. 2007)	
Sulforaphane (Choi et al. 2014)	
Shepherin I (polypeptide) (Park et al. 2000)	G-Y-G-G-H-G-G-H-G-G-H-G-G-H-G-G-H-G-G-H-G-G-H-G-H-G-G-G-G-H-G
Shepherin II (polypeptide) (Park et al. 2000)	G-Y-H-G-G-H-G-G-H-G-G-G-Y-N-G-G-G-G-H-G-G-H-G-G-G-Y-N-G--G-G-H-H-G-G-G-G-H-G
Oxalic acid (Grosso et al. 2011)	

(continued)

Table 14.13 (continued)

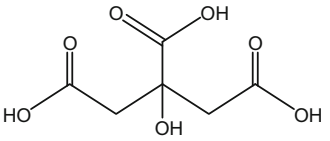
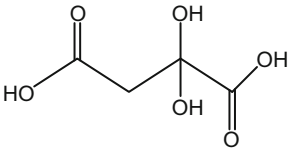
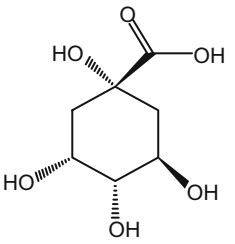
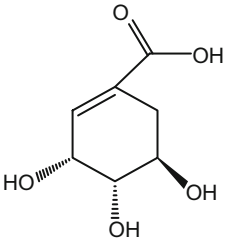
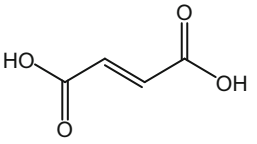
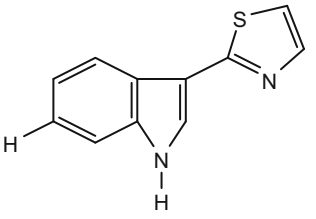
Constituent	Structure
Citric acid (Grosso et al. 2011)	
Malic acid (Grosso et al. 2011)	
Quinic acid (Grosso et al. 2011)	
Shikimic acid (Grosso et al. 2011)	
Fumaric acid (Grosso et al. 2011)	
	

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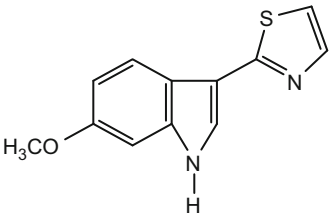
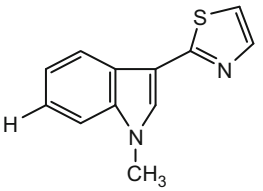
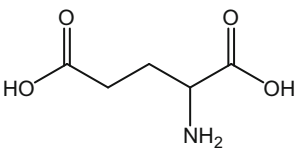
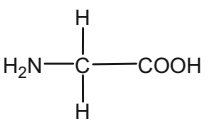
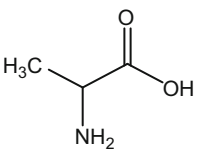
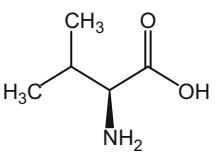
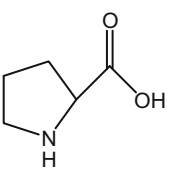
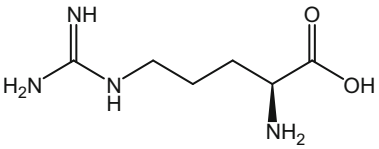
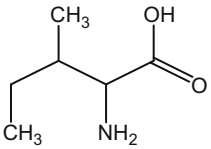
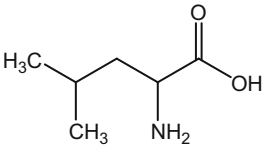
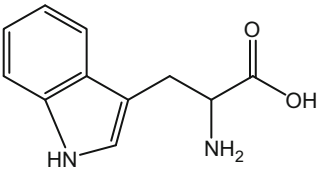
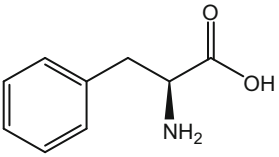
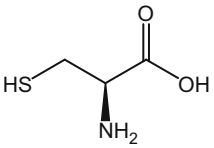
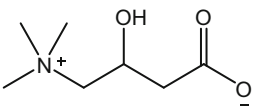
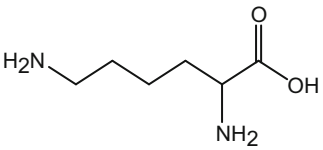
Table 14.13 (continued)

Constituent	Structure
6-Methoxycamalexîn	
N-methylcamalexin	
Glutamic acid (Grosso et al. 2011)	
Glycine (Grosso et al. 2011)	
Alanine (Grosso et al. 2011)	
Valine (Grosso et al. 2011)	
Proline	

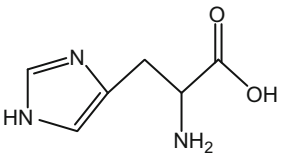
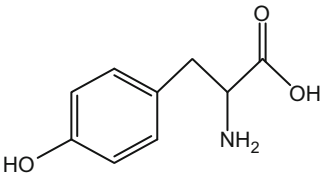
(continued)

Table 14.13 (continued)

Constituent	Structure
Arginine	
Isoleucine	
Leucine (Grosso et al. 2011)	
Tryptophan (Grosso et al. 2011)	
Phenylalanine (Grosso et al. 2011)	
Cysteine	
Carnitine (Grosso et al. 2011)	
Lysine	

(continued)

Table 14.13 (continued)

Constituent	Structure
Histidine (Grosso et al. 2011)	
Tyrosine (Grosso et al. 2011)	

crude protein, crude fiber contents (%), K, P, Mn, Fe, Cu, and Cd concentrations were high in *C. bursa -pastoris*. Also the values for pH, Na, Mg, Ca, S, Zn, and Pb were evaluated (Tables 14.10 and 14.11) (Tuncturk et al. 2015).

The nutritional composition of *C. bursa-pastoris* constitute minerals, vitamin A, ascorbic acid, proteins, linoleic acid, and omega-3-polyunsaturated fatty acids, and provide some beneficial effects to the human health (Guil-Guerrero et al. 1999; Zennie and Ogzewalla 1977).

Other studies show the isolation and identification of nearly 45 compounds, which account for about 71.53% of total content of essential oils, and among these essential oils palmitic (28.32%), phytane (10.15%), oleic acid (8.63%), and octacosane (4.73%) represent the main components (Yu et al. 2009).

In another study, 19 compounds were isolated from essential oil that accounts for 88.24% of total essential oil content, and which includes 1,1-dimethylcyclopentane, ethyl linoleate, palmitic acid, and phytane as main compounds (Tables 14.12 and 14.13) (Kamali et al. 2015a, b).

14.4 Conclusion

Selected scientific studies on the plant *C. bursa-pastoris* are given in a comprehensive way in this chapter. By using the significant scientific evidence-based studies especially preclinical studies data by considering the extensive use of this plant in traditional and complementary medicine. This plant is rich in constituents and has a wide range which are responsible for different pharmacological actions. Due to the safety and effectiveness profile of extracts from *C. bursa-pastoris*, this plant and its constituents can be used for development of new drugs for treating and managing many diseases. Of the conditions investigated, it appears that *C. bursa-pastoris* has commonly been investigated for its antimicrobial, anticancer, anti-inflammatory,

antioxidant, hepatoprotective, acetylcholine–esterase inhibition activities, besides have effects on smooth muscles, infertility effect, cardiovascular effects, sedative effects, effects on psoriasis, and multiple sclerosis. The positive scientific-based findings seen in this chapter are because of the crude extracts used in these studies which are rich in bioactive constituents. Plant extracts contain a wide range of bioactive compounds is a well-known fact and show their effects on body organs/tissues by variety of ways. Quercetin, icaritin, sinensetin, kaempferol-3-O-rutinoside, capselloside, kaempferol, quercetin-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside,kaempferol-7-O-α-L-rhamnopyranoside, quercetin-6-C-β-D-glucopyranoside, 7S,8R,8′R-(−)-lariciresinol-4,4′-bis-O-glucopyranoside, kaempferol-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside and kaempferol-3-O-rutinoside, lariciresinol4′-O-β-D-glucoside, (+)-pinoresinol-β-D-glucoside, salidroside, 3-(4-β-D-glucopyranosyloxy-3,5-dimethoxy)-phenyl-2E-propanol, β-hydroxy-propiovanillone 3-O-β-D-glucopyranoside, coniferin, 4′,7-dihydroxy-5-hydroxymethy-8-prenylflavonoid, β-sitosterol, luteolin, loliolide, 4′,7-dihydroxy-5-hydroxymethy-6,8-diprenylflavonoid, licoflavonol, Chrysoeriol-7-O-β-D-glucopyranoside, Acacetin-7-O-β-D-glucopyranoside, methyl-1-thio-β-D-glucopyranosyl disulfide, 10-methylsulphinyl-decanenitrile 11-methyl-sulphinyl-undecanenitrile, 1-O-(lauroyl) glycerol, phytene-1, 2-diol, (3S,5R,6S,7E)-5,6-epoxy-3-hydroxy-7-megastigmen-9-one, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone, 1-feruloyl-β-D glucopyranoside, pinoresinol-4′-O-β-D-glucopyranoside, quercetin-3-O-β-D-glucopyranoside, and luteolin 6-C-β-glucopyranoside are the phenolics and flavonoids compounds isolated from *C. bursa-pastoris*. Also, phytosterol compounds include stigmasterol, campesterol, lupeol, cholesterol, β-sitosterol, cholest-5-en-3-one, ergosta-4, 6, 8, 22-tetraen-3-one, stigmasta-3,5-dien-7-one, stigmasta-4-en-3-one were also isolated from *C. bursa-pastoris*, besides some fatty acids, organic acids, and amino acids.

Though there are only few studies which showed the evaluation of pharmacological potential of these phytoconstituents, as in most of the studies only methanolic and aqueous crude extracts are used. The use of crude extracts provides a rough idea about any pharmacological activity, as it is difficult to understand whether the activity is due to one single constituent or a synergistic action between different phytoconstituents. In additional to this, the process of extraction used for preparation of crude extracts and polarity of solvent leads to different phytoconstituents which makes comparison between different studies very cumbersome. During compiling this chapter, heterogeneous results were observed and in some studies results were conflicting, because the results of some studies are not reproducible. Also, some studies devoid of knowledge which makes free assessment of the therapeutic properties of the herb difficult. For an author, it is important to provide copious details related to experimental specifications, protocols, and also ensure thorough standardization of materials and other techniques, as few studies were devoid of this in current chapter. These overall pharmacological actions of *C. bursa-pastoris* need cautious interpretation. Mechanism studies, molecular analysis, larger sample sizes, and toxicological studies are some of the aspects which need to be considered for this plant. These studies are correlating the phytochemicals with pharmacological

activities. The studies on understanding the interaction between phytoconstituents from *C. bursa-pastoris* and their targets. Finally, for confirmatory decisions, there is the need of more robust scientific methodologies about the potential use of *C. bursa-pastoris*, which is the main key point before considering any clinical trials.

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15 Ethnopharmacology, Phytochemistry, and Biological Activities of *Achillea millefolium*: A Comprehensive Review

Saika Bashir, Aneeza Noor, Mohammad Iqbal Zargar, and Nasir Ali Siddiqui

Abstract

More than half of the population in developing nations depends on natural medication for treatment of different sicknesses and problems. Among them, *Achillea millefolium* from Asteraceae family is one restoratively significant plant called as "*yarrow*" and revealed as being utilized in folklore medication for sicknesses, for example, skin irritations, convulsive, hepatobiliary, and gastrointestinal issues. Monoterpenes are the most delegate metabolites, establishing 90% of the fundamental oils comparable to the sesquiterpenes, and a wide scope of chemical compounds have likewise been found. Distinctive pharmacological examinations in numerous in vitro and in vivo models have demonstrated the capability of *A. millefolium* with anti-inflammatory, antiulcer, anticancer activities, and so forth loaning help to the reasoning behind various of its conventional uses. Because of the essential pharmacological activities, *A. millefolium* will be a superior alternative for new medication discovery. Our chapter extensively gathers late phytochemical and pharmacological activities of *A. millefolium*, and should, accordingly, act as an appropriate reference for future investigation into the plant's phytochemical profiling and by and large pharmacological assessment.

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Keywords

Achillea millefolium · Phytochemistry · Therapeutic uses · Pharmacology · Constituents

15.1 Introduction

The *Achillea* genus has a place with the family Asteraceae, contains more than 130 enduring spice species native from Europe to Asia toward the Northern Hemisphere, and fills in calm atmospheres in semi-dry or dry territories (Si et al. 2006). One of the utmost, inescapable variety and the most normally and traditionally utilized variety of plant in society as well is *A. millefolium* L. (Radusiene and Gudaityte 2005). In India, it is widely known as Biranjasipha, Puthkanda, (Hindi), Rojmaari (Marathi), Achchilliya (Tamil), (Cavalcanti et al. 2006), Brinjasuf (Urdu), Yarrow (English) (Karmenderes and Apaydin 2003; Stojanović et al. 2005; Si et al. 2006; Lazarević et al. 2010; Tajik et al. 2008; Fierascu et al. 2015).

A. millefolium has a place with Asteraceae family constitutes the biggest group of Tracheophyta. It can grow up to 50 cm, and is erect along a thin underground part from which new aboveground growth produces long runners with an unpolished, delicious squama at every node. The leaves are bipinnate or tripinnate, and are 5–20 cm in length, practically fluffy, show high variance in shagginess, and are arranged close to the center spirally and lower part to the stems. Blossoms are ordinarily white color, but can be amaranthine or pink blossoms, having convex inflorescence with flowers having stalks and thick petals organized in smoothed groups. Fruits are approximately 2 mm, glossy, with comprehensively winged edges and no pappus (Akram 2013).

Aerial parts of Yarrow have generally been utilized as tea to treat fits, stomach-related objections, and different illnesses. The plant has a customary significance as ladies' spice, utilized as an emmenagogue and to decrease feminine pain (Benedek and Kopp 2007). It has likewise been utilized to treat dyspepsia, hunger, and stomach torments that present as issues (inward application) just as to lighten pelvic pain in ladies (effective application in sitz shower). The pharmacological action is ascribed to sesquiterpene lactones, flavonoids,and particularly azulene, which is the primary constituent of basic oil. Most of the pharmacological activities are due to the presence of flavonoids, as flavonoids and their derivatives are known to possess antioxidative, spasmolytic, choleretic, and antimicrobial activity. A lot of flavonoids present have a place with the class of flavones and flavonols, and their glycosides as luteolin, apigenin-7-O-glucoside, luteolin-7-O-glucoside, apigenin, and rutin (Bocevska and Sovová 2007).

15.2 Medicinal Importance of *A. millefolium*

A. millefolium is known as an amazing therapeutic plant around the world. Since earlier times, it has been utilized for wounds, stomach-related issues, respiratory ailments, and skin conditions. *A. millefolium* flavonoids (apigenin and luteolin) have been distinguished as the fundamental pharmacologically dynamic components (Applequist and Moerman 2011). Studies have demonstrated that luteolin secures rodents against psychological dysfunction (Liu et al. 2014), and furthermore against learning shortages in Alzheimer's disease (Schmidt and Wink 2017). It has been indicated that apigenin is viable in different neurologic problems, for example, sleep deprivation, Parkinson's disease, and neuralgia (Patil et al. 2014). The aerial parts of *A. millefolium*, a notable animal varieties among different individuals from Achillea, are normally utilized in European and Asian customary medication for the treatment of gastrointestinal problems and hepatobiliary grievances, just as for wound mending and skin inflammations (Jaradat 2005; Ugulu et al. 2009).

Iranian locals broadly utilized *A. millefolium* in medication to treat different illnesses including irritation, inflammations, and digestive problems. Notwithstanding, the dried flowers mixture is viewed as reasonable for hemorrhoids treatment, gastrointestinal problems, and menstrual abnormality (Miraldi et al. 2001). Italians utilize *A. millefolium* for an assortment of problems, including urinary and menstrual problems and essentially for gastrointestinal disorders (Passalacqua et al. 2007). The plant is locally employed for treating wounds in Hungary (Applequist and Moerman 2011; Bussmann et al. 2007) showed that in Peru *A. millefolium* is utilized for gastritis, diabetes, cardiovascular, and also as topical application under the names of Milenrama and Chonchón, Moreover, in Brazil it is mostly employed as a treatment for wounds, skin issues, diarrhea, and other diseases that occurs in gastrointestinal tract, with label name as Erva-de-cortaduras and mil-folhas (Baggio et al. 2008; Pires et al. 2009). Also, the mixture of plant or the aerial parts of the plants extract can be used as a sedative (Manfrini 2009). It has been widely used for treatment of wounds, hemorrhoids, varicose veins, menstrual problems, and various respiratory diseases (Applequist and Moerman 2011). *A. millefolium* as per Indian Ayurveda Pharmacopeia can be used as an antipyretic and to treat wounds. People of India use the leaves and blossoms for digestive issues (Sharma et al. 2004).

15.3 Taxonomy

European locals employ *A. millefolium* and incorporate three of the subspecies of *A. millefolium* including subspecies *millefolium* (little blossoms white), bloomed pink subspecies *alpestris* (Wimm. and Grab.), and subspecies *ceretanum* Sennen (large blossoms white) (Applequist and Moerman 2011). Ploidy shown by various species of *A. millefolium* is hexaploid (Applequist and Moerman 2011). At species level, the North American *A. millefolium* species has been perceived as *A. lanulosa* Nutt. Some of the time isolated into different species or at the sub-specific level as *A. millefolium* subsp. *lanulosa* (Nutt.) Piper. As barely characterized, this taxon is

tetraploid (Ehrendorfer and Guo 2006; Gervais 1977), while North American populaces perceived by certain specialists as *A. borealis* Bong. might be tetraploid or hexaploid (Ehrendorfer and Guo 2006; Ramsey 2007).

A. millefolium comes under the following taxonomical classification categories according to the United States Department of Agriculture's "Plant Database."

Domain	*Eukarya*
Kingdom	*Plantae*
Phylum	*Anthophyta*
Class	*Magnoliopsida*
Order	*Asterales*
Family	*Asteraceae*
Genus	*Achillea*
Species	*A. millefolium*

Domain: Eukarya—This area incorporates organisms with a genuine nucleus, containing hereditary material and layer-bound organelles.

Kingdom: Planta—This kingdom incorporates multicellular organisms that have chloroplast and perform photosynthesis to acquire supplements. Furthermore, these organisms have a cell wall made of cellulose and use a variation of age's life cycle.

Phylum: Anthophyta—This phylum, otherwise called Magnoliophyta, comprises of plants with a flowering body that produce seeds inside an amplified ovary or fruit. These life forms additionally have vascular tissue as a method for supplement transport.

Class: Magnoliopsida—This class incorporates cultivated plants comprising of an undeveloped organism with combined cotyledons and net-veined leaves.

Order: Asterales—This order remembers plants for which the ovary is inferior, flowers are conceived in involucrate, and it has spiraling flowering heads. At the point when the calyx is available, it is customized into a bunch of fruit covers called the pappus.

Family: Asteraceae—This family incorporates plants with a flowering head containing a thickly pressed bunch of some little, singular flowers, otherwise called florets.

Genus: *Achillea*—This genus obtained its name after the legendary Greek character, Achilles, who supposedly found the therapeutic wonders of this plant (Thieret 2001).

15.4 History

The genus *Achillea* name originates from the Trojan legend "Achilles," which means a healing of wound cure (Benedek et al. 2007).

A. millefolium is one of the most ancient, well-known botanicals utilized by people (Sensu *Lato*). It is among the six therapeutic plants whose dust was found in a *Homo neanderthalensis* grave at Shanidar, dated to 65,000 B.P. (Leroi-Gourhan

1975; Solecki 1975). Dioscorides portrayed the spice *achilleios*, or *millefolium* (among different names), as being valuable to stop bleeding, including from wounds and unusual menstrual bleeding and decrease irritation; a decoction could be utilized as a douche for menstrual bleeding and to be consumed for dysentery (Osbaldeston and Wood 2000).

In marine prehistoric studies, it has been revealed that *A. millefolium* examination is used for genetic examination purposes, including the DNA examination performed by Robert Fleischer at the Smithsonian Institution and sorted by the Institute for the Preservation of Medical Traditions. Their examination probably recognized a few of the tablets fixings, all considered in compositions of an opportunity to be therapeutic; notwithstanding yarrow, the investigation discovered DNA proof of radish, celery, parsley, carrot, cabbage (Applequist and Moerman 2011).

A. millefolium for a long time has been utilized as customary home grown medication (Eghdami and Sadeghi 2010). It has significant therapeutic potential (Applequist and Moerman 2011) and has been utilized in conventional medication for a very long time as natural teas for migraines, lotions for external uses for treating skin irritation, hepatobiliary disorder, gastrointestinal objections, and wound healing (Cavalcanti et al. 2006; Benedek et al. 2008; Nadim et al. 2011) (Table 15.1).

Table 15.1 Conventional uses of *A. millefolium* in various countries

S. no	Culture	Treatment	References
1	European	Gastroenteric conditions, lack of hunger, inflammation of the skin, wound healing, and external bleeding	Wichtl (2002, 2004)
2	Iranian	Pain and stomach conditions, hemorrhoids, acid indigestion, menstrual abnormalities, gastroesophageal reflux, and inflammation	Miraldi et al. (2001)
3	Peru	Diabetes, gastritis, cardiovascular problems, and skin disease	Bussmann et al. (2007)
4	China	Snakebite, dysmenorrhea, varicose veins, hemorrhoids, parches, and tuberculosis	Applequist and Moerman (2011)
5	Hungary	External ailments, burns, and wounds	Applequist and Moerman (2011)
6	India	Gastrointestinal issues and as an antipyretic	Sharma et al. (2004)
7	Brazil	Wounds, problems with the skin, diarrhea, and gastrointestinal issues	Baggio et al. (2008), Pires et al. (2009)
8	Italy	Menstrual complications, such as urinary or diuretic problems, toothache, tranquilizer and gastroenteric disorders	Applequist and Moerman (2011)

15.5 Phytochemistry of *A. millefolium*

With studies on *A. millefolium* synthetic constituents, it was possible to follow *A. millefolium* back to the nineteenth century, and several compounds were identified not long ago. Detailed active ingredients in *A. millefolium* below is summed up in Table 15.2.

15.5.1 Essential Oils

The most delicate metabolites monoterpenes establishing 90% of the fundamental oil of *A. millefolium* which correspond to the sesquiterpenes. But that as it may, because of different variables identified due to difference in chemical phenotype, distinct geographic variety, for example, temperature, day length, relative humidity, and composition of powerful variety in volatile oil. In addition, hereditary foundation might be a point answerable of influencing the composition of plants secondary metabolites (Zahara et al. 2014).

Table 15.2 Phenols from various parts of *A. millefolium*

S. no.	Phenols	References
1	Choline	Borrelli et al. (2012)
2	1,3-Dicaffeoylquinic acid (DCQA) and luteolin 4-O-glucoside	Vitalini et al. (2011)
3	1,4-Dicaffeoylquinic acid, apigenin 4-O-glucoside	Vitalini et al. (2011)
4	3,4-Dicaffeoylquinic acid (DCQA)	Benedek et al. (2007), Vitalini et al. (2011)
5	3,5-Dicaffeoylquinic acid	Innocenti et al. (2007), Benedek et al. (2007), Didier et al. (2011), Vitalini et al. (2011)
6	1, 5-Dicaffeoylquinic acid (DCQA)	Didier et al. (2011)
7	4, 5-Dicaffeoylquinic acid (DCQA)	Benedek et al. (2007), Didier et al. (2011)
8	Luteolin-7-β-D-O glucuronide	Benedek et al. (2007)
9	Caffeic acid	Tunón et al. (1994), Wojdyło et al. (2007), Yasa et al. (2007), Pires et al. (2009)
10	Ferulic acid	Tunón et al. (1994), Wojdyło et al. (2007)
11	Stachydrine, salicylic acid, pyrocatechol, adenine, 2-hydroxy-2-phenylacetic acid (mandelic acid)	Tunón et al. (1994)
12	Methyl esters of caprylic-linolenic p-coumaric acid and undecylenic acid	Wojdyło et al. (2007)
13	Chlorogenic acid	Tunón et al. (1994), Innocenti et al. (2007), Vitalini et al. (2011), Benetis et al. (2008), Didier et al. (2011)

15.5.2 Phenols

The phenols detailed from various parts of *A. millefolium* are discussed in the Table 15.2.

15.5.3 Flavonoids

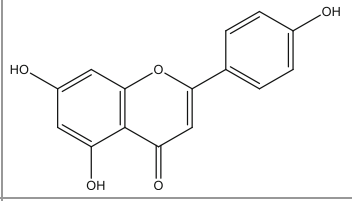
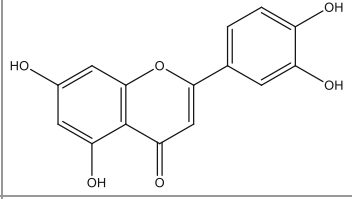
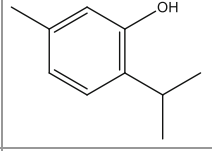
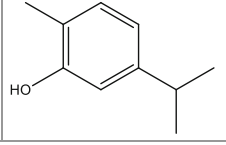
A. millefolium include flavonoids including casticin, apigenin, centaureidin, quercetin, rutin, luteolin, isorhamnetin, artmetin, and acacetin some of which are shown along with their structures in Table 15.3 (de Souza et al. 2011). It also contains (cosmosiin) apigenin 7-O-glucoside (cynaroside), luteolin 7-O-glucoside (Vitalini et al. 2011; Benedek et al. 2007; Yasa et al. 2007; Schulz and Albroscheit 1988; Oswiecimska and Miedzobrodzka 1966; Horhammer 1961; Michaluk 1962; Kaloshina and Neshta 1973; Horhammer 1961), and achillinin A (Li et al. 2011), luteolin and apigenin (Innocenti et al. 2007; Csupor-Löffler et al. 2009; Benedek et al. 2007; Wojdyło et al. 2007; Guédon et al. 1993), luteolin-7-O-β-D-glucopyranoside, dihydrodehydrodiconiferyl alcohol 9-O-β-D-glucopyranoside, luteolin-4-O-β-D-glucopyranoside, and apigenin-7-O-β-D-glucopyranoside (Innocenti et al. 2007), 5-hydroxy 3,40, 6,7-tetramethoxy flavones (Gadgoli and Mishra, 2007; Falk et al. 1975), isorhamnetin (Wojdyło et al. 2007; Falk et al. 1975), and acacetin (Greger, 1969). Glycoside flavonoids and Aglycone flavonoids such as C-glycosylflavones, flavone O glycosides and flavonol are also present in *A. millefolium*. The aglycone flavanoids include neptin, chrysophanol D, hispidulin, centauridin, quercetagetin, cirsimarin, and salvigenin. Glycoside flavanoids consist of swertisin, vicenine, swertiajaponin, and vitexin.

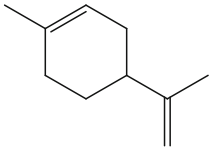
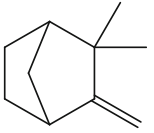
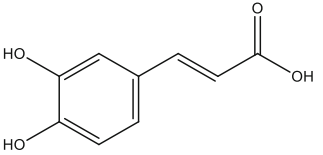
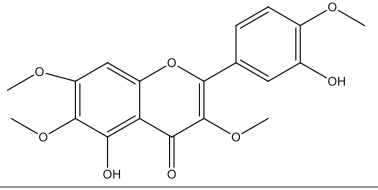
The flavone-O-glycosides and flavonol include quercetin-3-O-glycoside, diosmetin-7-O-glycoside, kaemferol-3-O-glycoside quercetin-3-O-rhamnoglycoside and luteolin-7-O-glycoside (Ivancheva et al. 2002).

15.5.4 Sesquiterpenes

Sesquiterpene lactone diol, sesquiterpene lactone ester B, and sesquiterpene lactone ester A (Farooq et al. 2012), seco-pseudo guaianolides (Csupor-Löffler et al. 2009), azulenogene sesquiterpene lactones namely 8-acetoxy-artabsine, 8-angeloxy-artabsine and 2,3-dihydro-desavetoxymatricin (Verzár-Petri et al. 1979) achimillic acids A, B & C (Tozyo et al. 1994) are some of the sesquiterpenoids present in *A. millefolium*. The sterols comprise of stigmasterol, campesterol, β-sitosterol, and cholesterol; on the other hand, triterpenes spotted are α-amyrin, taraxasterol, β-amyrin, and pseudo-taraxasterol (Chandler et al. 1982). Sesquiterpenes containing oxygen comprised the highest portion of the essential oil, epi-cubenol (18%) the main portion of that fraction. Sesquiterpene hydrocarbons (22%) another considerable fraction, out of which delemene (7%) is the main component.(Dall'Acqua et al. 2011).

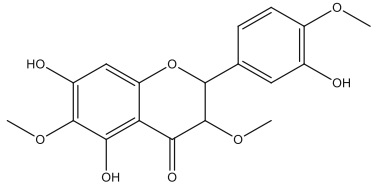
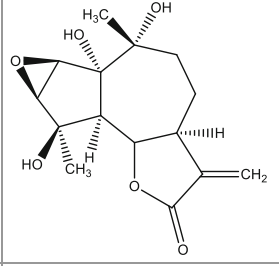
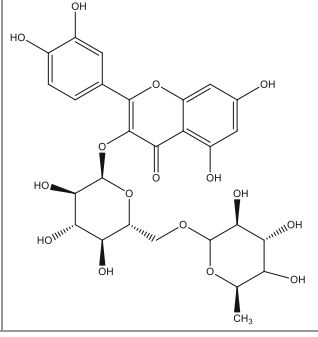
Table 15.3 Various phytochemicals and their structures reported from *A. millefolium*

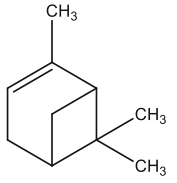
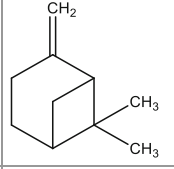
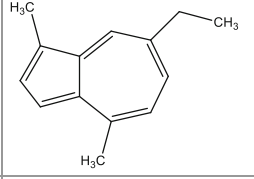
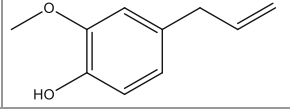
S. no.	Compound	Molecular formula	2D structure
1	Apigenin	$C_{15}H_{10}O_5$	
2	Luteolin	$C_{15}H_{10}O_6$	
3	Thymol	$C_{10}H_{14}O$	
4	Carvacrol	$C_{10}H_{14}O$	

5	Limonene	$C_{10}H_{16}$	
6	Camphene	$C_{10}H_{16}$	
7	Caffeic acid	$C_9H_8O_4$	
8	Casticin	$C_{19}H_{18}O_8$	

(continued)

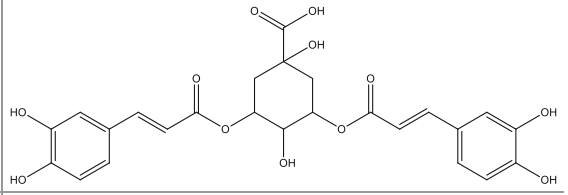
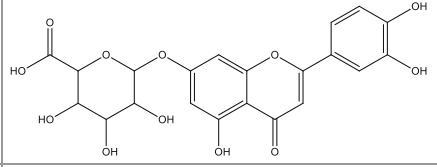
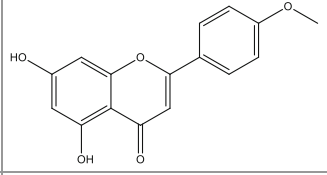
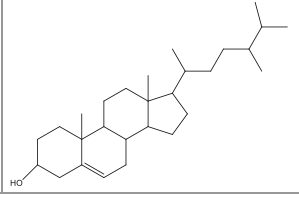
Table 15.3 (continued)

S. no.	Compound	Molecular formula	2D structure
9	Centaureidin	$C_{18}H_{16}O_8$	
10	Achillinin A	$C_{15}H_{20}O_6$	
11	Rutin	$C_{27}H_{30}O_{16}$	

12	α-Pinene	$C_{10}H_{16}$	
13	β-Pinene	$C_{10}H_{16}$	
14	Chamazulene	$C_{14}H_{16}$	
15	Eugenol	$C_{10}H_{12}O_2$	

(continued)

Table 15.3 (continued)

S. no.	Compound	Molecular formula	2D structure
16	3,5-Dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	
17	Luteolin-7-*O*-glucuronide	$C_{21}H_{18}O_{12}$	
18	Acacetin	$C_{16}H_{12}O_5$	
19	Campesterol	$C_{28}H_{48}O$	

20	Cholesterol	$C_{27}H_{46}O$	
21	β Stigmasterol	$C_{29}H_{48}O$	

15.5.5 Hydrocarbon Monoterpenes

P-cymene (Ebadollahi et al. 2016; Zeinivand and Yousefzadeh 2013; Nadim et al. 2011; Orav et al. 2006; Jaimand et al. 2006); β-phellandrene, α-pinene, and β-pinene (Sevindik et al. 2016; Kazemi 2015; Costescu et al. 2014; Falconieri et al. 2011; Nadim et al. 2011; Conti et al. 2010; Bimbiraitė et al. 2008; Orav et al. 2006; Nemeth 2005; Boskovic et al. 2005; Rohloff et al. 2000; Hofmann et al. 1992); α-thujane, α-terpinene, and γ-terpinene (Maz et al. 2013); cis-Chrysanthenol (Judzentiene 2016), limonene, and camphene (Kazemi 2015; Nadim et al. 2011; Bimbiraitė et al. 2008); and sabinene (Boskovic et al. 2005; Conti et al. 2010; Nadim et al. 2011) are the hydrocarbon monoterpenes present in *A. millefolium.*

15.5.6 Oxygenated Monoterpenes

Piperitone (Ebadollahi et al. 2016); bornyl acetate, borneol, and camphor (Kazemi 2015; Conti et al. 2010; Maz et al. 2013; Ebadollahi et al. 2016; Boskovic et al. 2005; Candan et al. 2003; Sevindik et al. 2016; Rahimmalek et al. 2009); carvone and carvacrol (Kazemi 2015); terpinen-4-ol and α-terpineol (Sevindik et al. 2016; Nadim et al. 2011; Candan et al. 2003), include some of the monoterpenes isolated from *A. millefolium.*

15.5.7 Oxygenated Sesquiterpenes

Sellin-11-en-4α-o-l, viridiflorol, 10 epi-γ-eudesmol, and bisabolol oxides (Judzentiene 2016), umbelulone (Zeinivand and Yousefzadeh 2013; Costescu et al. 2014; Orav et al. 2006; Nemeth 2005) are some of the oxygenated sesquiterpenes identified in *A. millefolium.*

15.5.8 Sesquiterpene Hydrocarbons

Bicyclogermacrene (Rahimmalek et al. 2009), β-cubebene (Costescu et al. 2014), β-caryophyllene (Sevindik et al. 2016; Costescu et al. 2014; Conti et al. 2010; Orav et al. 2006; Bezić et al. 2003), α-asarone and β-bisabolene (Falconieri et al. 2011), cadinene and α-humulene (Bimbiraitė et al. 2008), Germacrene-D-4-ol and Germacrene (Lourenco et al. 1999) are the sesquiterpene hydrocarbons identified in *A. millefolium* (Table 15.3).

15.6 Pharmacological Activity of *A. millefolium*

15.6.1 Anti-Inflammatory Activity

Significant mediators including arachidonic acid metabolic products are liable for causing inflammation. Especially lipoxygenase result of this pathway assumes a significant part in inflammation. Arachidonate is oxidized to 5-hydroperoxyeicosatetreonic acid (a PUFA polyunsaturated unsaturated fat) by a chemical called arachidonate 5-lipoxygenase which catalyzes its transformation forming the main result of arachidonate course which in succession lead to leukotriene biosynthesis. These are responsible for a group of activities that incorporate the initiation and maintenance of different inflammatory diseases, and its hindrance has been found to help the inflammatory activity of most of the medications. Thus, in light of the logical statement, an enzymatic bioassay soybean 15-lipoxygenase was utilized by Trouillas et al., to observe the anti-inflammatory activity of different plant components. *A. millefolium* came out to be one of the victorious therapeutic plant competitors with an eminent capacity to restrain lipoxygenase action.

A. millefolium along with 16 different extracts were assessed against B16 melanoma cells of mouse (C57BI/6 mouse spontaneous skin tumor cells) for cytotoxic effect evaluation. The results concluded that at a significantly low concentration ($<$0.25 mg/mL), out of all the plant extracts evaluated for cell proliferation after 2 days, only *A. millefolium* extract along with nine other plants showed pro-proliferative activity. However, at a concentration $>$0.5 mg/mL, significant anti-proliferative properties was observed in six extracts, including *A. millefolium*, among others (Pain et al. 2011).

Another evidence of anti-inflammatory activity was evaluated on ethanoic extract in olive and sunflower oil. The assay based on the application of the extract on irritated skin by sodium lauryl sulfate revealed that aerial parts of *A. millefolium* are responsible for possessing remarkable activity (Lopes et al. 2021).

The chronic inflammatory disease is atopic dermatitis (AD) that usually affects the skin and is difficult to cure completely. Topical calcineurin inhibitors which are included in the AD therapy are the ointment of corticosteroids and tacrolimus and have many side effects on the skin as well as on the rest of the body. Thus, meditations of natural origin are used increasingly in the development of AD therapy *A. millefolium* is thus used as a conventional medicine to cure inflammation and to treat wounds. Ethanolic extract of *A. millefolium* rich in caffeic acid, chlorogenic acid, and rutin, has shown its efficacy against atopic dermatitis (Ngo et al. 2020).

An assay based on THP-1/M cells by MTT method, revealed that supercritical antisolvent fractionation (SAF) of III *A. millefolium* extract showed anti-inflammatory activity, although separation fraction being more potent action than precipitation vessel ones (Chou et al. 2013).

15.6.2 Antioxidant Activity

For examining the antioxidant prospects of different extracts of AM accepted chemical and biological assays have been employed. Interestingly, both qualitative and quantitative analysis of some important phenolics present in *A. millefolium* was done by using HPLC. Based on HPLC–DPPH assay, the significant antioxidant activity was observed in *A. millefolium* due to the presence of higher content of phenolic compounds (Innocenti et al. 2007) as shown in Table 15.4. The total content of phenolic compounds of AM varies at different growth stages. At IC50, its antioxidant activity was reported, and reduction of IC50 value is the notable marker of increasing essential oil ability to act as DPPH scavenger. During the plant growth period, its antioxidant activity gradually decreased, and in the harvested plants at the vegetative (25.54 mg mL^{-1}) and flowering (25.87 mg mL^{-1}) stages significantly were higher than harvested plants at the fruit set stage (Farhadi et al. 2020).

Table 15.4 Various phytochemicals of A. *millefolium* and their pharmacological properties

S. no.	Phytochemical	Pharmacological effect	Reference
1	Luteolin 7-O-glucoside and apigenin 7-O-glucoside	Antiparasitic, anti-inflammatory and antioxidant	Vitalini et al. (2011), Yasa et al. (2007)
2	Quercetin	Spasmolytic	Lemmens-Gruber et al. (2006)
3	Rutin	Antioxidant and antinociceptive	Pires et al. (2009), Vitalini et al. (2011)
4	Pyrocatechol	Antiparasitic	Tunón et al. (1994)
5	Achimillic acids A, B and C	Anticancer	Tozyo et al. (1994)
6	Caffeic acid	Antioxidant, antiparasitic	Tunón et al. (1994)
7	Achillinin A	Inhibits the growth of tumor cells	Li et al. (2011)
8	Chlorogenic acid	Antiparasitic and antioxidant	Didier et al. (2011), Tunón et al. (1994)
9	Casticin, Centaureidin	Suppresses growth of tumor cells	Csupor-Löffler et al. (2009)
10	Psilostachyin C, sintenin, desacetylmatricarin, isopaulitin and paulitin	Antiproliferative	Csupor-Löffler et al. (2009))
11	5-Hydroxy 3,4,6,7 tetramethoxy flavone	Prevent damage of a liver	Gadgoli and Mishra (2007)
12	Luteolin-7-O-β-D glucuronide	Act as choleretic	Benedek et al. (2006)
13	Bisabolol	Immunosuppressive	Saeidnia et al. (2004)

15.6.3 In Vitro Estrogenic Activity

Its in vitro estrogenic activity was evaluated on methanol/water fraction of the crude plant extract. The assay based on MCF-7 revealed that in particular it's the aerial parts of AM that are involved in its notable activity than other parts of the plant from the extracts. On performing sequential liquid–liquid chromatography (LLE), with increasing polarity it was shown that the most potent estrogenic fraction is the methanol/water (Benedick and Kopp 2007).

15.6.4 Antiulcer Activity

By the oral administration of hydroalcoholic extract of AM at a dose ranging from 30 to 300 mg/kg, gastric lesions introduced by ethanol were inhibited to 35, 56, and 81% and at a dose of 1 mg/kg and 10 mg/kg, respectively; chronic gastric ulcers induced by the administration of acetic-acid were reduced to considerable 43 and 65%. Furthermore, this dose is also proven to have a beneficial effect on gastric mucosa regeneration followed by gastric ulcer induction. This effect was established by conducting immune-histochemistry assay using proliferating cell nuclear antigen (PCNA) with positive results which in turn hint at increased cell proliferative effects of AM. Furthermore, the hydroalcoholic extract of AM also revealed a significant lowering of SOD and GSH levels that usually elevate after acetic acid–induced gastric lesions (Saluk-Juszczak et al. 2010).

The damage to the epithelium of the oral cavity, pharynx, and a gastrointestinal tract by the chemotherapy or radiotherapy treatment of malignancies is characterized under oral mucositis (Mehdipour et al. 2011). It has been seen that *A. millefolium* has played an important role to treat it. Rashidi et al., in their study, concluded that *A. millefolium* has shown marked results in the healing of rats' gastric ulcers (Miranzadeh et al. 2014). Miranzadeh et al. studied that *A. millefolium* distillate solution is effective in the treatment of chemotherapy-induced oral mucositis and stomatitis (Zayachkivska et al. 2005).

Potrich FB et al. in its in vivo study concluded that chronic gastric ulcers can be reduced by hydroalcoholic extract of AM and also probably because of its antioxidant properties it can promote notable transformation of the gastric mucosa (Potrich et al. 2010).

15.6.5 Hypotensive Activity

Studies done on rats under anesthesia revealed that the aqueous–methanolic extract of aerial parts of *A. millefolium* brings about a dose-dependent (1–100 mg/kg) reduction in blood pressure of arteria. The phytochemical extract of *A. millefolium* brings about negative metabotropic outcome in continuously beating atrial tissues of guinea pig. These results revealed that *A. millefolium* exerts a hypotensive effect (Khan and Gilani 2011).

Lourenco et al. considered the outcome of *A. millefolium* on anesthetized rat and assessed that different extracts as dichloromethane (DCM), ethyl acetate (EA), dicholomethane-2 (DCM-2), and hydroethanolic extract (HEAM) fractions, in addition to the isolated flavonoid and artemetin, exerted their hypotensive effect. Other studies let out that on oral administration of three extracts as DCM (20 mg/kg), HEAM (100–300 mg/kg), DCM-2 (1030 mg/kg) has considerably decreased the mean arterial pressure (MAP) of normotensive rats, while no such effect was noticed from the ethyl acetate (10 mg/kg) extract (de Souza et al. 2011).

Based on the assaying of artemetin against the cardiovascular effect of both bradykinin and angiotensin I, the biomolecular basis of the antihypertensive effect of *A. millefolium* was carried out based on mechanistic studies of artemetin. The study revealed that the mean extent of bradykinin-prompted antihypertensive effect was increased by artemetin injection at a dose of 0.75 mg/kg, while the hypertensive reaction to angiotensin I was also significantly reduced (de Souza et al. 2011).

15.6.6 Antimicrobial Activity

In an in vitro study by Ferda Candan et al. on the essential oil of *A. millefolium*, it was detailed that it revealed average effect in case of *Clostridium perfringens, Streptococcus pneumonia*, and *Candida albicans*, and less marked effect in case of *Candida krusei*, *Acinetobacter lwoffii*, and *Mycobacterium smegmatis* as the existence of eucalyptol (1,8-cineole), borneol, and camphor, familiar antimicrobial agents (Candan et al. 2003).

Due to the presence of terpenes such as camphor and 1,8-cineol in the essential oil of *A. millefolium* its antimicrobial potential was unmasked. In addition to the antimicrobial activity was also probably related to the presence of terpenes like carvone, thymol, eugenol, terpinene and p-cymene (Burt, 2004). Chemical compounds were detected on performing chromatographic analysis of *A. millefolium* essential oil and the content detected was 0.4%. The hydrocarbon sesquiterpene class was in abundance (74.29%). The most abundant chemical compound was α-farnesene (31.66%), followed by chamazulene (17.17%), β-caryophyllene (10.27%), and sabinene (8.77%). With minimum inhibitory concentration for all species above 1.5 mg mL^{-1}, the AM presented low antimicrobial activity against the analyzed species S. *epidermidis*, *C. albicans*, *E. coli*, and *K. pneumoniae* probably because among the chemical compounds known in the literature for their pronounced antimicrobial potentials, only eucalyptol was present with a low concentration of 1.96% (Daniel et al. 2020).

15.6.7 Anti-Spermatogenic Activity

The anti-spermatogenic potential of ethanolic extract of AM was evaluated in male rats, which revealed significant decrease in fertility parameters. There was no marked variance in sperm viability and sperm motility body weight by the amount

of 200–400 mg/kg/day for 50 days. Although, body weight of 200 mg/kg reduction was noticed in weight of epididymis, daily sperm production (DSP), epididymal sperm reserve (ESR), and testosterone concentration. It is clear from the result that alcoholic concentrate of *A. millefolium* possess antifertility result, which may be attributed to the presence of its chemical constitution but its mechanism is not clear (Parandin and Ghorbani 2010) (Table 15.4). Besides these few more pharmacological properties have been provided in Table 15.4.

15.7 Toxicity and Interaction

A. millefolium partakes in a number of interactions with organisms going from insects to humans. Especially, *A. millefolium* shows various harmonious interactions with encompassing organisms. Moreover, as *A. millefolium* is a photosynthetic plant, it goes about as an essential maker of energy on the base levels of the food chain. At the point when it comes being utilized as a food source, this plant is eaten by the two herbivores and omnivores, and its energy is moved further up the evolved way of life to secondary and tertiary consumers. In view of its wealth, yarrow is a fundamental energy vital for various organisms all through an assortment or biological activities. As referenced before in reproduction, *A. millefolium* participates in a mutualistic relationship with numerous pollinators. In this harmonious relationship, the two species are profited on the grounds that the yarrow plant is being pollinated which considers its multiplication cycle to turn up at ground zero, and the pollinators, thus, are given an excellent source of food.

Moreover, *A. millefolium* is associated with another mutualistic relationship with individuals from the parasites phylum Glomeromycota. These Glomeromycota parasites structure endomycorrhizae with yarrow, which means the growth develops inside the yarrow roots and sends its hyphae into the root cell dividers. This close connection takes into consideration the plant to get more water, gases, and different supplements from the organism. Consequently, the organism gets sugars that are put away inside the plant cells. The last cooperation and fundamental explanation behind considering this plant species is yarrow's relationship with people as a mending operator. Yarrow has been utilized as an ethnobotanic for a very long time. Going back to ancient Greece and times when just clans meandered North America, *A. millefolium* has had a critical impact in the lives of people, both at that point and now, with regards to its therapeutic attributes. Reaping methods of yarrow have continued as before consistently. To gather yarrow as a therapeutic subject, one may reap the whole plant during its blossoming months, or collect just the leaves past to the plant's blooming months (Schwartz 2006).

It has been noted that *A. millefolium* can be safely used to treat various ailments in medicinal amounts, although allergic patients may feel irritation when AM comes in contact with skin (Ijaz et al. 2020).

Risk factors related to long exposure to *A. millefolium* have not been entrenched. Even though, the Food and Drug Administration has categorized the plant as innocuous and has given the approval of utilizing in alcoholic drinks. Some noxious

effects had been noted after its use in animal studies and on human exposure (Guédon et al. 1993).

Higher doses of *A. millefolium* ethanolic extract given at 56 times higher than human doses in pregnant rats indicated not one abortifacient, contraceptive, nor teratogenic effect (Boswell-Ruys et al. 2003).

Graf et al. in their studies found that *A. millefolium* tea had a poor genotoxic effect due to the presence of flavonoids (Graf et al. 1994).

Another evidence regarding toxicity of *A. millefolium* has suggested that due to the existence of compounds including guaianolides (one of the category of sesquiterpenoid) and mostly alpha-peroxyachifolid present at variable concentrations might cause allergic contact dermatitis in some people (Rücker et al. 1991). Although concentration may decline in dried extract because of deterioration of various constituents (Hausbn et al. 1991).

15.8 Conclusion

The transcending studies suggest that *A. millefolium* is known as an amazing therapeutic plant around the world. *A. millefolium* flavonoids (apigenin and luteolin) have been distinguished as the fundamental pharmacologically dynamic components. Studies have demonstrated that apigenin is viable in different neurologic problems, for example, sleep deprivation, Parkinson's disease, and neuralgia. *A. millefolium* is a significant therapeutic plant of medication under Unani system also. Besides flavonoids, *A. millefolium* contains various essential oils; phenols; sesquiterpenes like 8-acetoxy-artabsine, 8-angeloxy-artabsine, achimillic acids A, B & C, etc.; and other phytochemicals which possesses a number of pharmacological activities including anti-inflammatory and antioxidant activity as their main pharmacological activities. *A. millefolium* has emerged as better alternative for the treatment of various disease in recent years. Yet the study that have been done to determine the efficacy of *A. millefolium* and their phytoconstituents in prevention and treatment of various diseases is slightly confined. Further investigations are required to validate the effectiveness and potency of this plant.

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A Review on Traditional Uses, Phytochemistry, and Pharmacological Activities of *Verbascum thapsus*

16

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Abstract

Verbascum thapsus is annual or biennial herb, which belongs to the family Scrophulariaceae. It has becomes naturalized in most temperature regions of the world, where it can be found in abundance on roadsides, meadows, and pasture lands. The plant *V. thapsus* is commonly known as "*Mullein.*" *V. thapsus* has a broad native range including Europe, North Africa, Western and Central Asia. It has been introduced to Japan, Sri Lanka, the United States of America, Australia, and New Zealand. The herb has been utilized as a medicinal herb since ancient times, and has a great potential to treat a number of ailments. Mullein is supposed to be loaded with significant number of bioactive constituents including triterpene, tetraglycosides, saponins, terpenes, flavonoids, carotenoids, tannins, carbohydrates, phenolic acid, sugars, proteins, and minerals. Due to the presence of these potent phytoconstituents, it has been traditionally used as a folk medicine for a majority of locals in different parts of world. Reported literature of the plant available from primary and secondary search engines unveil a number of pharmacological activities of the plant, including antitumor, cardiovascular, anti-inflammatory, hepatoprotective, antibacterial, antiviral, nephroprotective,

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anthelmintic, analgesic activity, etc. The aim of this chapter is to provide a comprehensive review of the various therapeutic activities of the plant along its phytochemical constituents which are responsible for its medicinal status.

Keywords

Verbascum thapsus · Mullein · Scrophulariaceae · Phytochemical moieties · Pharmacological profile

16.1 Introduction

The genus *Verbascum* L. is usually known as mullein, is a member of family Scrophulariaceae, which includes more than 400 wide-reaching species. Forty-five species (Rami-Porta et al. 2007) and a few fusions of *Verbascum* exist in the plants of Iran, 20 of which are widespread (Rechinger 1981; Sotoodeh et al. 2017). This class includes *Verbascum thapsus* L., which grows wild on flinty ground, in woodland, wasteland, clearings, and along the side of roads (Speranza et al. 2010). Plants of this type are generally utilized in tradition medicine (Gvazava and Kikoladze 2007). Its small yellow flowers are grouped solidly on a tall stem, which rolls from a large rosette of leaves. It flourishes in a wide diversity of habitats, but opt for ablaze anxious soils, where it can emerge promptly after the ground experiences light, from long-standing seeds that continue in the soil seed bank. It is a usual weedy from its large rosette of leaves. It flourishes as a wide diversity plant that proliferates by industriously producing seeds, but hardly becomes assertively insidious, because its seeds need open ground to sprout. It is a very insignificant obstacle for most agricultural crops, cause it is not a very aggressive species, being fanatical of shade from other plants and impotent to endure tilling. It also acts as a host for many insects, many of these can be dangerous to various plants. Even though those are effortless to detach by hand, populations are burdensome to abolish permanently (Watts 2000). *Verbascum* is thought to be a derivative of "barbascum," from the Latin *barba*, meaning moustache, referring to the genus' disheveled occurrence, while *Thapsus*, its particular name, may refer to the Greek island of the same name, where the species once flourished. The word "mullein" is derived from Middle English moleyne and Old French *moleine*, as well as the Latin *mollis*, which means "soft" and refers to the leaves (Le Strange 1977). There are 360 species of common mullein, also recognized as Wooly Mullein (*V. thapsus* L.) (Faik and Zeki 2008). *V. thapsus* L. also called as Kharghwug (Murad et al. 2011), Ghordoughkaro (Hussain et al. 2007), Gidder Tambakoo (Qureshi et al. 2007), Tamakusak (Shinwari and Gilani 2003), Khardhag (Sher et al. 2011), Jungle Tambako and Barbasco (Sher et al. 2011). Different chemical constituents have been isolated like saponins—triterpene B, triterpene A, saikogenin A (De and De Pascual 1978), thapsuine B, hydroxythapsuine, thapsuine A, hydroxythapsuine A iridoid glycosides—harpagide, verbascoside A, aucubin and isocatalpol, and their various derivatives (Bianco et al. 1984; Seifert et al. 1985b) and phenylethanoid glycosides (Warashina et al. 1991,

1992). Flavonoids have also been isolated from the plant (Souleles and Geronikaki 1989). *The Verbascum* types enclose photochemical including iridous (Arrif et al. 2008) phenylethanoids (Brownstein et al. 2017), flavonoids (Nykmukanova et al. 2019), neolignan glycosides (Akdemir et al. 2004), saponins spermine alkaloids (Halimi and Nasrabadi 2018) mucilage (Saeidi and Lorigooini 2017), vital oils, and fatty acids (Alipieva et al. 2014; Riaz et al. 2013; Boğa et al. 2016). Phenolics are another foremost group of the plants compounds that have revealed several biological results, including antibacterial and antioxidant actions against reactive oxygen species (ROS), particularly superox (Nègre-Salvayre and Salvayre 1992; Tauchen et al. 2015; Arsene et al. 2015; Carvalho et al. 2018; Rasera et al. 2019).

16.2 Historical Background of *V. thapsus*

The *Verbascum* gets its name from the Latin word "*barbascum barba*" (Jankowiak 1976), which refers to the plant's beard-like filaments (Wilhelm Jr 1974). The word *Thapsus* may have been extracted from the Isle of Siclian *Thapsos*, where mullein was collected in ancient times (Mitich 1992), or from the Tunisian island *"Thapsus*," according to legend (Jankowiak 1976). Instead of the yellow flower of the plant, *Thapsos* is a Greek term (Wilhelm Jr 1974). The plant has yellow flowers, and the Roman ladies have yellow hair. Mullein is derived from the Latin word *mollis*, which means soft (Durant 1976), and is synonymous with the modern term woolen (Mitich 1992; Notch 1989). Although the exact history of its introduction into North America is unclear, *V. thapsus* (common mullein, Scrophulariaceae) was most likely presented into North America multiple times, both inadvertently and deliberately as a remedial herb in California (Gross and Werner 1978).

By 1880, *V. thapsus* had arrived in Siskiyou county (Watson 1880), and herbarium assemblage began in the early 1900s. Not a thing is noted about the timing and specimens of its proliferation throughout the area, but it was discovered in 1934 at 1615 m in the Tahoe National Forest and has likely occupied some high-elevation locations for not less than seven decades (CalFlora Database, http://www.calflora.org). The wildflower *V. thapsus* is an alarming roadside and industrial pest (Semenza et al. 1978). However, since it is mostly found only in disturbed areas, it has not been identified as a significant toxic intruder in most parts of California (Hoshovsky 1986). *V. thapsus*, on the other hand, may form dense stands in areas with thin soils and open undergrowth, or in wooded areas after a fire. In the Owens Valley, it is said to have displaced native herbs and grasses in whole meadows.

16.3 Botany

V. thapsus is a stiff and stout herbaceous annual or biennial wild blossom. It produces a low rosette with a height of up to 61 cm. Flowers are closely packed and appear one per axil, in both male and female reproductive organs. Flowers have five sepals, five petals, a two-celled ovary, and five stamens and are yellow in color.

Fruit is a capsule that splits into two halves as it reaches adulthood. The capsule has a star-shaped facade and is ovoid in shape, measuring 3–6 mm in length. The pits are brown in color and range in length from 0.5 to 1.0 mm. In general, the basal leaves are oblong-obviate to oblanceolate entire, with small and extended petioles (10–40 cm). The leaf borders are alternately arranged and are either whole or unclearly crenate. Cauline leaves are 5–30 cm long with pinnate venation and are arranged along the stem. Mullein has an extensive taproot and a fibrous, thin secondary root system. The stem is upright and robust, with a size range of 50–180 cm. The stalk is usually plain, with leaves arranged in a row (Halvorson and Guertin 2003; Wagner et al. 1999).

16.4 Medicinal Importance of *V. thapsus*

Historically, mullein has been employed as an antidote for the respirational tract, mostly in cases of annoying coughs with bronchial blocking (Hoffmann and Manning 2002). Mullein leaves and flowers have expectorant and demulcent effects, which are employed by herbalists to cure respiratory complications for example bronchitis, dry coughs, whooping cough, tuberculosis, asthma, and harshness (Turker and Gurel 2005; Berk 1996). The flowers are gently diuretic and have a gentle and anti-inflammatory properties on the urinary area. The leaves are also diuretic, potion to reduce inflammation of the urinary system, and oppose the irritating effect of acid urine (Ambasta 1986; Turker and Camper 2002). Some herbal texts extend the remedial use to pneumonia and asthma (Turker and Gurel 2005). The leaves, roots, and the flowers are also anodyne, antibacterial, antispasmodic, astringent, emollient, nerving, vulnerary, analgesic, antihistaminic, anticancer, antioxidant, antiviral, bacteriostat, cardiodepressant, estrogenic fungicide, hypnotic, and calming (Harris 1972; Lucas 1969; Turker and Gurel 2005). The demulcent and emollient properties originate from the polysaccharide adhesive and gums that mitigate the bothered tissue. The expectorant property is the result of aspirins that stimulate fluid production. The anti-inflammatory property is due to ericoid glycosides and flavonoids that decrease tenderness (Turker and Gurel 2005). The mullein combines the expectorant exploit of its saponins with the gentle effect of its mucilage, making this a most valuable herb for the behavior of huskiness, tight coughs, bronchitis, asthma, and whooping cough (Turker and Gurel 2005). The dehydrated leaves are occasionally smoked in a common tobacco pipe to reduce the annoyance of the respiratory mucus membrane, and will totally restraint the hacking cough of utilization. The leaves are engaged with similar advantages when made into cigarettes, for asthma and irregular coughs. The flowers placed in a bottle and set in the sunshine are said to defer a fatty matter valuable as a cure for hemorrhoids. Fomentations and poultices of the leaves have been noticed helpful in hemorrhoidal complications. Mullein is said to be of much worth in diarrhea, from its amalgamation of demulcent with a strict effects and this amalgamation reinforcement of the entrails at the same time (Turker and Gurel 2005). In Europe, a sweetened infusion of flowers strained in order to separate the rough hairs is used as a domestic remedy

for mild catarrhs and colic. A preserve of the flowers has also been working antagonistic to ringworm, and a purified water of the flowers was long alleged to be a treatment for erysipelas and burns (Prakash et al. 2016; Turker and Gurel 2005). A decoction of leaves was employed as a health stimulant. A decoction of roots febrifuge is used to improve toothache and also to alleviate cramps, convulsions, and migraines. The cordial of the plant and powder made from the dehydrated roots is said to rapidly separate irregular warts while massaged on them (Tyler 1994). An oil formed by macerating mullein flowers in olive oil, stored in a corked bottle during extended subjection to the sun, or by placing it near the fire for some days, is employed as a local preparation in country districts in Germany for piles and other mucus membrane inflammation, and also for frostbite and bruises. Mullein oil is prescribed for earache and discharge from the ear, and for any eczema of the external ear and its duct (Turker and Gurel 2005). Mullein oil is a beneficial demolisher of disease germs (Chopra et al. 1956; Prakash et al. 2016). The additional plants, marinated for 21 days in olive oil, are reported to make an commendable bactericide. An alcohol color is formulated by homoeopathic chemists, from the new herb with spirits of wine, which has demonstrated advantageous for migraines or sick annoyances of long status, with authority of the ear (Bianchini and Corbetta 1977; Lewis and Elvin-Lewis 2003). The seeds of mullein are reported to be toxic and should not be employed in any of these researches (Berk 1996). The seeds when thrown into the water are said to intoxicate fish, and are employed by pillagers for that motive, being a little narcotic. Major toxic rudiments disturbing the circulatory, respiratory, and central nervous systems of the fish comprise spooning, rotenone, and glycoside. The common mullein causes fish to have complexity in breathing (Wilhelm Jr 1974). The flowering stem was employed, dehydrated out by Greeks and Romans as a candle immersed in tallow for light. Mullein torches were reported to repel witches. There is authentication that at one time, it was a "magical plant" of the ancients. Agrippa, a general and priest under Caesar Augustus, reported that the aroma from the leaves had an ungovernable effect on demons. Mullein was believed to be an element in drinks and love potions, and introduced in magic spells used by witches during the Middle Ages. The women of Rome also infused the flowers and mixed the ensuing liquid with lye, using it as a clean to turn their hair golden yellow (Le Strange 1977).

16.4.1 Antitumor Activity

FO-Com (plants extracted from *V. thapsus* in pure olive oil) revealed antitumor activity. Aqueous extricate from *Densiflorum* blossom had a significant restraint result on the expansion stage of protein biosynthesis in isolated rat liver microsomes when tested for antitumor property. The saponin fraction was found to be the key culprit (Turker and Camper 2002).

16.4.2 Cardiovascular Activity

Verbacoside (1 mm) enhanced heart rate by 37%, contraction force by 9%, and coronary perfusion rate by 68% in isolated, perfuse rodent hearts (Langendorff model). As compared to the spirited α-adrenergic blocker phentolamine (1 μM), verbascoside remarkably enhanced chronotropism ($p = 0.010$), tropism ($p = 0.016$), and CPR ($p = 0.016$) (Mehrotra et al. 1989).

16.4.3 Anti-inflammatory Activity

The anti-inflammatory activity of verbascoside is possibly due to its capability to scavenge nitric oxide radicals. J774.1 cells were stimulated by seven phenylethanoids, involving acteoside (verbascoside), at concentrations of 100–200 mm compact (6.3–62.3%) nitrite assemblage in lipopolysaccharide (0.1 μg/mL). They decreased nitrite assemblage caused by lipopolysaccharide (0.1 mg/mL), interferon (100 U/mL) in mouse peritoneal evacuate macrophages by 32.2–72.4% at 200 mm. In human polymorphonuclear leukocytes, verbascoside inhibited the development of the 5-lipoxygenase product 5-HETE and leukotriene B. The critical scavenging properties of verbascoside (acteoside) were very high (Kimura et al. 1987).

16.4.4 Hepatoprotective Activity

Aucubin managed intravenously at 100 mg/kg substantially confined beagle dogs from mortal poisoning generated by digestion of *Amanita virosa* mushrooms. The action of aucubin was partially because of a defensive conclusion on the despair of m-RNA biosynthesis in the liver due to α-amanitin intoxication. It has also been revealed that aucubin confined mice from hepatic impairment produced by carbon tetrachloride intoxication (Pandey et al. 1982).

16.4.5 Antibacterial Activity

In the current study, typical plant namely *V. thapsus* has been evaluated against selected human pathogens for its antimicrobial properties. The reports showed that the plant extracts tested have important antibacterial potential in opposition to *Escherichia coli*, *Yersinia pestis*, *Pseudomonas aeruginosa*, *B. cereus*, *Listeria monocytogenes*, *and Staphylococcus aureus* (Table 16.1) (Kannan et al. 2009; Prakash et al. 2016).

Table 16.1 Taxonomic hierarchy of *Verbascum thapsus*

Taxonomic hierarchy	
Rank	Scientific name and common name
Kingdom	Plantae—plantes, Planta, Vegetal, plants
Subkingdom	Viridiplantae—green plants
Infrakingdom	Streptophyta—land plants
Superdivision	Embryophyta
Division	Tracheophyta—vascular plants, tracheophytes
Subdivision	Spermatophytina—spermatophytes, seed plants, phanérogames
Class	Magnoliopsida
Superorder	Asteranae
Order	Lamiales
Family	Scrophulariaceae—figworts, scrofulaires
Genus	*Verbascum* L.—mullein
Subspecies	*Verbascum thapsus* ssp. thapsus L; common mullein

16.4.6 Treatment of *Trichomonas vaginalis*

Acceptance of apoptosis in *Trichomonas vaginalis* due to the remove of this plant have been reported by Kashan et al. Inhibitory concentration 50% (IC50) of ethanolic abstract of *V. thapsus* and metronidazole later 24 h were 39.17 and 0.0326 μg/mL, respectively. Outcomes of this study specify that the percentage of apoptosis after behavior of parasites with various concentrations of *V. thapsus* extricate (25, 50, 100, 200, and 400 μg/mL) were 20.7, 37.04, 47.5, 62.72, and 86.35 respectively (Kashan et al. 2015).

16.4.7 Antiviral Activity

When tested for antiviral property antagonistic to Herpes simplex Virus Type-1 (HSV-1) and influenza virus A (using dye-uptake assay systems), *V. thapsus* lyophilized flower infusion showed potent anti-influenza property with IC50 $<$ 6.25 mg/mL (Rajbhandari et al. 2009). In vitro cells, Zanon et al. discovered that an ethanolic extricate of *V. thapsus* had the greatest restraint effect antagonistic to pseudorabies virus strain RC/79 (*Herpes suis*) (2 log). The same types were reported to prevent plaque genesis induced by pseudorabies by 50% at a concentration of 35 μg/mL, 59 and 99% inhibition during the adsorption process, and virus development with the plant extract in a follow-up study (Escobar et al. 2012). Antiviral activity of *V. thapsus* against influenza virus (IC50 $<$ 6.25 mg/mL) is also encouraging (Rajbhandari et al. 2009). Another antiviral study using methanol extracts of 100 plants in opposition to 7 viruses found 12 extricates to be effective antiviral agents at concentrating that were also noncytotoxic. In this analysis, extracts from *V. thapsus* were found to inhibit the herpes virus type-1 (Mccutcheon et al. 1995), particularly decoctions from the flowers of *V. thapsus*, which revealed

very powerful effect in opposition to viruses (Mehrotra et al. 1989; Zanon et al. 1999). Although there have been no attempts to separate and estimate antiviral property of active metabolites from the ethanolic/methanolic decoctions of *V. thapsus*, a few studies on main metabolites from other plants with a high tendency to be avoided in the previous solvent decoctions have been allowed. In one study, verbascoside was observed to be most potent in opposition to respiratory syncytial virus (RSV-A2), with an EC50 of 0.80 μg/mL, an IC50 of 76.9 μg/mL, and a variability index (SI) of 85.4 (Chen et al. 1998). Aucubin, an iridoid glycoside, isolated from *Plantago asiatica* plants, was tested for antiviral property in opposition to a hepatitis B viral culture system (Hep G2 cells). While aucubin had no antiviral activity on its own, when it was preincubated with glucosidase, it showed promising results (Chang 1997).

16.4.8 Nephroprotective Activity

As compared to normal silymarin (50 mg/kg), the methanolic extract of *V. thapsus* leaves showed a nephroprotective protective effect in rats against gentamicin-induced nephrotoxicity at doses of 250 and 500 mg/kg. A drop in creatinine, urea, and urea nitrogen in the blood levels indicated a substantial reduction in nephrotoxicity. These qualities can also contribute to its ethnomedicinal status as a diuretic (Kahraman et al. 2011), so more experimental verification of active ideologies of *V. thapsus* methanolic solvent fraction is crucial.

16.4.9 Anthelmintic Activity

When concentrated in methanol, several extricate from *V. thapsus* had anthelmintic and insecticidal effects in vitro. The earthworm (*Pheretima posthuma*) was employed to measure anthelmintic behavior, with the time of paralysis and death compared to the orientation medication albendazole. *V. thapsus* extract was used at various concentrations of 5, 10, 25, 50, 75, and 100 mg, and it was found to have a significant anthelmintic effect. Leaf and fruit concentrates killed the worms in 35 and 40 min, correspondingly Leaf extricate had substantial anthelmintic property than stem extract, and root extract had the least anthelmintic commotion, according to the average paralytic and death time (Ali et al. 2012).

16.4.10 Analgesic Activity

In a mouse model of acetic acid–induced writhing and tail pressure pain, the nociceptive inhibitory properties of verbascoside were investigated. *Verbascoside* had a major analgesic effect when measured at 300 and 100 mg/kg. *Verbascoside* also had sedative properties, prolonging pentobarbital-induced anesthesia and minimizing locomotion, both of which were aided by methamphetamine (Morina

et al. 2010). However, because of the sampling approach (only VB is used in these studies), the synergistic analgesic potential of all of the metabolites present in *V. thapsus* is largely unknown.

16.5 Phytochemistry

Glycoside, saponins, flavonoids, and terpenoids are the main phytoconstituents of *V. thapsus*. These phytoconstituents are partially or completely responsible for the pharmacological arrangements mentioned above. As a result, all phytoconstituents that have previously been inaccessible from *V. thapsus* are considered based on chemical categorization and the primary references of the fundamental studies mentioned.

16.5.1 Phenylethanoid Glycosides

A study of Warashina from *V. thapsus* was unable to access any phenylethanoid glycosides (H. Hussain et al. 2009). These include arenarioside, cistanoside B, alyssonoside, forsythoside B, 1′-O-β-D-(3-hydroxy-4-methoxy-phenyl)ethyl-α-L-rhamnopyranosyl-(1 → 3′)-β-D xylopyranosyl-(1 → 6′)-4′-O-feruloylglucopyranoside, 1′-O-β-D (3,4-dihydroxyphenyl)-ethyl-α-L-rhamnopyranosyl-(1 → 3′)3′- hydroxy-4′-O-β-D, glucopyranosyl-cinnamoyl-(1 → 6′) glucopyranoside,alyssonoside,1′-O-β-D-(3,4dihydroxy-phenyl)-ethyl-α-L-rhamnopyranosyl (1 → 3′)-β-D-xylopyranosyl-(1 → 6′)-4′-O-feruloylglucopyranoside, and leucosceptoside (Warashina et al. 1992). Ergosterol peroxide, docosanoic acid, oleanolic acid, and β-sitosterol were inaccessible from blossoms of *V. thapsus* (Milne and Abbott 2002).

16.5.2 Iridoid Glycosides

Verbascoside is a typical case of iridoid glycosides that were discovered much earlier than expected in the leaves of *V. thapsus* (Hattori and Shiroya 1951). The sum of aucubin, an iridoid glycoside, obtained from roots was significantly higher than segments (Seifert et al. 1985a). After segregation, an ethanolic extricate of the roots of *V. thapsus* that display anti-germination property on barley (*Hordeum vulgare*) kernels yields numerous iridoids containing harpagoside, ajugol, laterioside, and aucubin (Pardo et al. 1998). Isocatalpol, methylcatalpol (2 h), and 6-O-α-L-rhamnopyranosyl catalpol are some of the other iridoid glycosides that have been found. (Pardo et al. 1998). Warashina et al. spotted numerous iridoids from the entire herbal of V. thapsus, including 6-O-[3″-O-(3,4-dimethoxy-transcinnamoyl)] saccatoside, α-L-rhamnopyranosyl catalpol [6-O-(3′-O-p-coumaryl)-α-L-rhamnopyranosyl catalpol] (2m),6-O-(4″-O-p-coumaroyl) α-L-rhamnopyranosyl catalpol, verbascoside A, 6-O-[2″-O-(3,4-dihydroxy-trans-cinnamoyl)] α-L-rhamnopyranosyl catalpol, 6-O-[4″-O-(3,4-dihydroxy-trans-

cinnamoyl)]-α-L-rhamnopyranosyl catalpol,6-O-(2″-O-(p-methoxy-trans-cinnamoyl)-α-L-rhamnopyranosyl catalpol, 6-O-(4″-O-isoferuloyl)-α-L-rhamnopyranosyl catalpol, 6-O-(2″-O-isoferuloyl)-α-L-rhamnopyranosyl catalpol, 6-O-(2″-O-feruloyl)-α-L-rhamnopyranosyl catalpol, 6-O-(3″-O-(p-methoxy-trans-cinnamoyl)-α-L-rhamnopyranosyl catalpol, 6-O-(4″-Oferuloyl)-α-L-rhamnopyranosyl catalpol and 6-O-(3″-Oisoferuloyl)-α-L-rhamnopyranosyl catalpol (Turker and Camper 2002). Another iridoid, harpagide, was isolated from *V. thapsus* inflight sections (Stavri et al. 2006). Although as from whole herbal 5-O-α-L rhamnopyranosyl (1α-3)-[α-D-glucuronopyranosyl (1α-6)]-α-D-glucopyranoside was isolated (Pardo et al. 1998). Most recently ajugol (2f), ningpogenin, 10-deoxyeucommiol, jioglutolide, 6-β-hydroxy-2-oxabicyclo[4.3.0]-Δ8–9-nonen-1one, 8-cinnamoylmyoporoside, and verbathasin A were inaccessible iridoids (Zhao et al. 2011).

16.5.3 Triterpene Tetraglycosides

Kurodo et al. recognized five triterpene tetraglycosides from the methanolic extricate of *V. thapsus* blossoms: buddlejasaponin I, ilwensisaponin A, ilwensisaponin B, ilwensisaponin C, and buddlejasaponin IA (Kuroda et al. 2012).

16.5.4 Saponins

From *V. thapsus*, different saponins which include saikogenin A, triterpene A, saikogenin B, veratric acid, α-spinasterol, thapsuine A and B (4g-h), hydroxythapsuine-A, and 3-Ofucopyranosyl saikogenin have been reported and seperated (Turker and Gurel 2005; Turker and Camper 2002; Stavri et al. 2006). These constituents may have antimicrobial, antiviral, and antitumoral activity, according to the pharmacological profile of *V. thapsus.*

16.5.5 Terpenes

Two sesquiterpenes: buddlindeterpene A and B from northern Pakistan; one diterpene, that is, from China GC-MS investigation of *V. thapsus* displayed limonene (26.57%), cineole (7.24%), caryophyllene oxide (5.91%), pinene (4.72%) 5 g, from *V. thapsus* whole plant (Hussain et al. 2009), and essential to terpenes (Dzubak et al. 2006). These multiplexes can also play a role in *V. thapsus* pharmacological movement across a wide spectrum.

16.5.6 Flavonoids and Carotenoids

Flavonoids have the ability to counteract the effects of reactive free radicals, and as a result, they have a high standing in antioxidant, cancer, diabetes, and a diversity of other diseases associated to oxidative stress (Nijveldt et al. 2001). The leaf total phenolic content was 0.124 mg/g dry weight, stem 0.166 mg/g dry weight, and root total flavonoid content was 0.024 mg/g dry weight (Kogje et al. 2010). The configuration of flavonoids was investigated in the roots and aerial sections of plants, which are stems, leaves, blossoms, and seeds, from 22 *Verbascum* species (Kalinina et al. 2014). Seven flavonoids from *V. thapsus* were inaccessible: acacetin-7-O-D-glucoside, luteolin, cynaroside, kaempferol, quercetin, and rutin. A new flavonoid, apigetrin, has been discovered in a 70% aqueous acetone inflight concentrate (Zhao et al. 2011). Separation and classification of another new flavonoid, 4′7-dihydroxyflavone-4′-rhamnoside, as well as 6-hydroxyluteolin-7-glucoside and 3-′-methylquercetin, from the leaves and flowers of *V. thapsus* has also been identified (Souleles and Geronikaki 1989). Carotenoids, especially zeaxanthin, have been extracted from the seed oil of *V. thapsus* and may be used as dietary sources. Another research discovered that *V. thapsus* seed oils have relatively greater α-tocopherol levels, with a ratio of 1:10 for α- to γ-isomers (Jia et al. 2009).

16.5.7 Carbohydrates

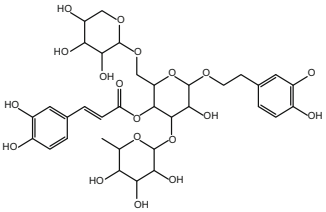
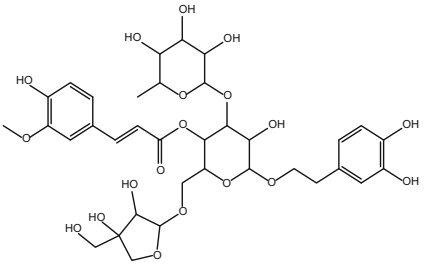
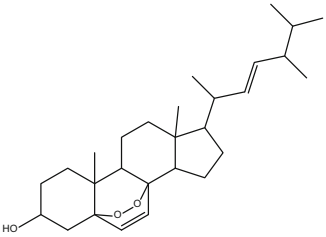
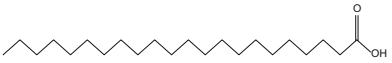
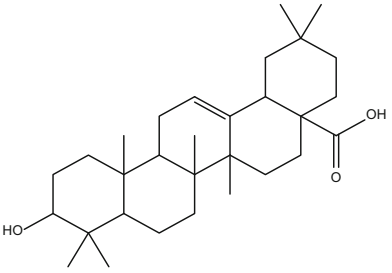
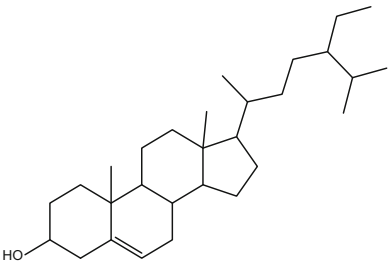
Verbascose, sucrose, hepatose, octaose, and nonaose are some of the carbohydrates isolated from *V. thapsus* (Turker and Gurel 2005; Hattori and Hatanaka 1958).

Some examples of constructions can be found in Table 16.2.

16.6 Toxicity Studies

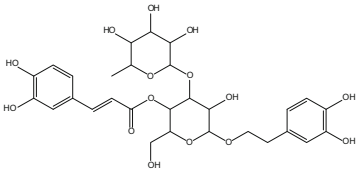
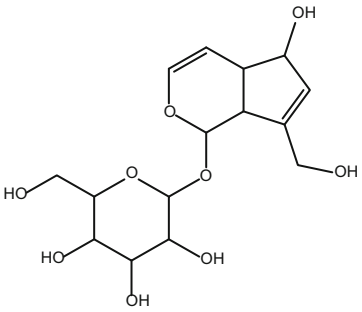
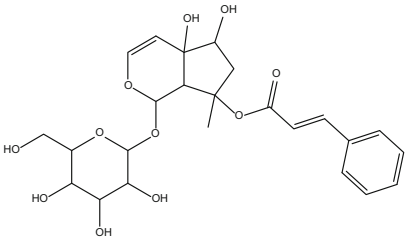
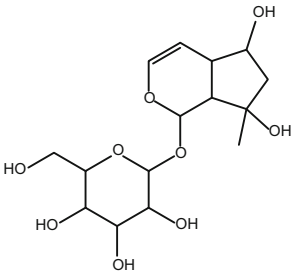
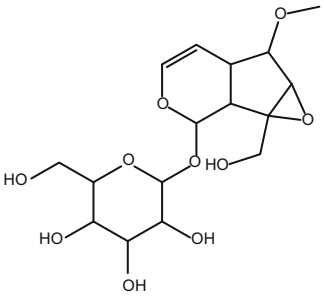
There is no details on the mullein flower's genotoxicity, carcinogenicity, reproductive, or developmental effects. The operation and toxicity of certain *V. nigrum* extricates and decoctions were investigated. The extracts of *V. nigrum* had a low toxicity profile. During the 72-h period following the supervision of doses up to 5000 mg/kg, no effect on mouse behavioral responses, and no cases of transience were noticed (Kalinina et al. 2014). A radish kernel and brine shrimp bioassay were used to assess the toxicity of various *V. thapsus* abstracts. At the higher doses of 1000 mg/dL, all of the extracts (water, methanol, and ethanol) were found to be healthy. Surprisingly, aqueous extract decoction was more toxic than distillation, suggesting that it may involve increased toxic complexes than other forms of extricates. A case study on the effects of a herbal drug amalgamation called CKLS (colon, kidney, liver, spleen) that contains *V. thapsus* as one of the main ingredients is very interesting. The patient developed severe kidney damage after a 5-day course of CKLS. Despite the fact that CKLS contains 10 other plant mixtures, further

Table 16.2 Structures of active constituents of *Verbascum thapsus*

Active constituents	Structure	References
Arenarioside		Milne and Abbott (2002)
Alyssonoside		Milne and Abbott (2002)
Ergosterol peroxide		Milne and Abbott (2002)
Docosanoic acid		Milne and Abbott (2002)
Oleanolic acid		Milne and Abbott (2002)
B-sitosterol		Milne and Abbott (2002)

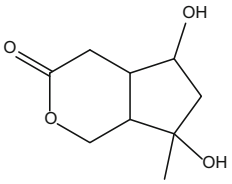
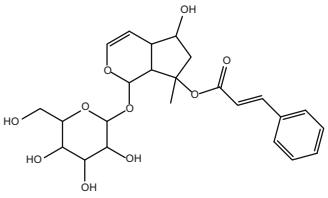
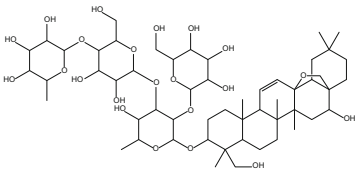
(continued)

Table 16.2 (continued)

Active constituents	Structure	References
Verbascoside		Zhao et al. (2011)
Aubucin		Zhao et al. (2011)
Harpagoside		Zhao et al. (2011)
Ajugol		Zhao et al. (2011)
Methylcatalpol		Zhao et al. (2011)

(continued)

Table 16.2 (continued)

Active constituents	Structure	References
Jioglutolide		Zhao et al. (2011)
8-Cinnamoylmyoporoside		Zhao et al. (2011)
Buddlejasoponin		Kuroda et al. (2012)

research is needed to rule out *V. thapsus* as a cause of nephrotoxicity, particularly because herbal drugs are frequently dismissed.

16.7 Conclusion

The multiple benefits of *V. thapsus* made it a true miracle of nature. It significantly possesses a variety of secondary metabolites, thus representing useful sources of bioactive compounds and preparation with healthy encouraging effects such as anti-inflammatory, hepatoprotective, nephroprotective, cardiovascular, antitumor, etc. The diverse effects of mullein are attributed to the presence of various triterpene, fatty acids, and phytosterols. The pharmacological investigation confirmed the empirical traditional application of mullein in humans for the treatment of digestive disorders, tumor formation, urinary tract infection, and certain skin diseases. Mullein evaluated for phytochemical constituents had great potential to act as a source of useful lead molecules and ameliorate health condition of consumers due to the presence of various bioactive compounds that are indispensable for good health.

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Acorus calamus: A Review on Its Phytochemical and Pharmacological Profile

17

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Abstract

By systematizing and analyzing the vigor of potent plant-derived compounds, herbal drugs can assist the exposure of a replacement period of the healthcare system to nurse human diseases within the future. Perception of lore and remedial plants can play a vital role within the utilization and revelation of natural plant resources. *Acorus calamus* is a tall perennial marshland monocot plant, being the member of the family Acoraceae. *A. calamus* habitually known as sweet flag It is also known by different names, including sweet sedge, sweet root, sweet rush, sweet cane, sweet myrtle, myrtle grass, myrtle sedge, gladdon, myrtle flag, flag root, and cinnamon sedge. This medicinal herb is perhaps native to India and located across China, Europe, northern Asia Minor, southern Russia, Japan, northern USA, Sri Lanka, Burma, and Japan. The rhizomes of calamus and aromatic leaves are conventionally employed as a drug and therefore the dried and powdered rhizome features a tangy flavor and is employed as an alternate for nutmeg, cinnamon and ginger for its odor. The rhizomes are examined to have carminative, expectorant, nauseate, nervine, sedative, stimulant, aromatic, anthelmintic, and antispasmodic properties, and also employed for the medicaments of mental ailments, epilepsy, antidiabetic, antioxidant, anticonvulsant, long-term diarrhea, dysentery, glandular and abdominal tumors, fevers, and bronchial catarrh. The prehistoric people of China employed it for constipation and to reduce swelling. In Ayurvedic School of medicine from India, the rhizomes are wont to treat various diseases like bronchitis, fever, asthma, and as a sedative. Indigenous tribes employed it to treat a cough. As a carminative they employed it to make a decoction from it and as an infusion for colic. Perception of lore and

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remedial plants can take part in vital role within the utilization and unearthing of natural plant assets. Encyclopedic approach and association are needed to take care of ancient documentation on medicinal plants and utilizing these assets in benefit of citizenry. The present review gives a brief introduction about the medicinal, phytochemical, and pharmacological related aspects of the plant.

Keywords

Acorus calamus · Expectorant · Ayurvedic · Antispasmodic · Aromatic

Abbreviations

Ac	*Acorus calamus*
API	Ayurvedic Pharmacopeia India
BHU	Banaras Hindu University
BP	Blood pressure
CCB	Calcium channel blockade
DPPH	2,2-Diphenyl-1-picrylhydrazyl
ECG	Electrocardiography
GABA	Gamma-amino butyric acid
HDL	High density lipoproteins
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IC	Inhibitory concentrations
LDL	Low density lipoproteins
LPO	Lipid peroxidation
MES	Maximal electroshock seizure
OPD	Out patient department
STZ	Streptozotocin
USA	United States of America

17.1 Introduction

During the past decade, herbal medicine gained lot of importance particularly in those developing countries where population depends on conventional specialists, remedial plants for their medical care needs. Besides the availability of modern medicine, herbal medicine retained its significance. With the increasing usage of herbal medicine, issues for their quality and efficacy also increased. Increased profits have forced the researchers to go through various conventional claims. In today's world everyone needs scientific recommendation before making use of the conventional drugs. Thus, information regarding medicinal plant as drug is recommended before its use. The present effort is to review and organize total information till date on *Acorus calamus*, a plant employed in the Indian School of medicine for various reasons. *A. calamus* (sweet flag) is the herbaceous perennial, and it is about 2 m tall (NRCS 2014). Its leaves are like those of Iridaceae. Sweet flag consists of the cluster

of leaves at the base and these leaves arise from the rhizome (NRCS 2014). The leaves are erect and yellowish-brown; the pattern of veination is parallel. By crushing it, fragrant odor is emitted out and that confirms the presence of spadix as shown in Figs. 17.1, 17.2, and 17.3. Besides "sweet flag" and "calamus" some other names include myrtle flag, myrtle sedge, myrtle root, beewort, gladdon, sea sedge, sweet cinnamon, sweet cane, sweet sedge, sweet grass, sweet root, sweet myrtle, and sweet rush (NRCS 2014; Runkel and Bull 2009).

Taxonomy: (Singh et al. 2011a, b)
Kingdom: Plantae
Subkingdom: Tracheobionta
Super division: Spermatophyta
Division: Magnoliophyta
Class: Liliopsida
Subclass: Arecida
Order: Arales
Family: Acoraceae
Genus: *Acorus* L.
Species: *Calamus*

Fig. 17.1 Aerial parts of *Acorus calamus*

Fig. 17.2 *Aerial parts of Acorus calamus*

Fig. 17.3 Aerial parts of *Acorus Calamus*

17.1.1 Habit and Ecology

A. calamus is a robust plant generally growing from tropical to subtropical climates. Sunshine is necessary for the growth of plant and also for drying the harvested rhizome from the plant. Temperature fluctuates from 10 to 38 °C and rainfalls ranging from 70 to 250 cm are the favorable conditions. Plantation should be evaded in places where there's no irrigation possibility. Light alluvial soil of river banks, clayey loams, and sandy loams are the favorable soils where *A. calamus* is usually planted (Chandra and Prasad 2017). It is allocated all over the tropics and subtropics of Sri Lanka and India especially. In marshy places of Himalayas, it grows up to 2000 m altitude (Balakumbahan et al. 2010). It is reported in the districts of Jammu and Kashmir (Sharma et al. 1985), Andhra Pradesh (Rao and Sreeramulu 1985), Karnataka (Malabadi et al. 2007), Himachal Pradesh (Jain and Puri 1994), and in districts of Uttar Pradesh (Srivastava et al. 1997).

Common Names

Sweet flag or calamus (NRCS 2014)

Vernacular Names

Arabic: bach, vaj, vajj

English: calamus, flag root, sweet flag, sweet cane, sweet rush (NRCS 2014; Runkel and Bull 2009)

Hindi: bacc, bach, baj, gora-bach, vasa

Sanskrit: bhadra, bacha, bhutanashini, bodhaniya

Urdu: waj-e-turki, bacha

Kashmiri: vai-gandur, vai

Habitat: *A. calamus* is a subaquatic herbaceous perpetual herb

17.1.2 Morphology

Leaves. Leaves are scented, lineal, upright, and cutlass, up to 1 m in length and 1–2 cm in width. The midvein is usually off center (Motley 1994).

Stem. The stem is resilient, creased, subterranean rhizome that ranges in length 10–35 cm and 1–2 cm in diameter, whitish-pink in color within, with distant nodes and internodes. They are very aromatic and bitter in taste (Motley 1994).

Roots. Roots are white, rarely branched, and produced in rows on the anterior side of crawling rhizome.

Inflorescence. The inflorescence comprises of a spathe and spadix.

Flowers. Flowers are perfect and hypogynous; green, densely crowded on a cylindric, sessile, spadix.

Fruit. The fruit is a multi-seeded mucilaginous berry (Fernald 1950).

Seeds. Seeds are oblong in shape (Motley 1994)

17.1.3 History and Folklore

A. calamus has a long and an interesting history. The name "Acorus" has descended from the Greek word *Acoron*, employed by Dioscorides, which in turn was descended from *Coreon* meaning "pupil" as it was employed in the treatment for inflammation of eye (Grieve 1971). Sweet flag has abundant chronicled history in the Indian and Chinese civilization. In Indian markets, sweet flag was introduced by Celsius without any impediment. In India, for centuries it was used as the significant remedial aid for stomach disorders and colic (Barton and Castle 1877). The rhizome of the plant was employed to cure diarrhea, dysentery, and asthma. It was believed by the Romans, Chinese, and the Arabians that the rhizome of *A. calamus* has aphrodisiac property (Connell 1965). They ate it raw with bread and boiled vegetables "for carnal desires" because it was said that this plant "excites the carnal cupidity for 'Venus'" (Wedeck 1960). Sweet flag was distributed from its native region to Europe by Mongols in eleventh century and is part of the herbs stated in *Exodus*. Soon, *A. calamus* became "symbol of invasion "of Mongols and was known as 'Mongolian poison'" as they planted them wherever they settled, because they believed *A. calamus* purified water. Austrian Botanist, Clusius acquired rhizome from Asia Minor, and planted it in Vienna and thus the first record of sweet flag cultivation was in 1954. In England, it was planted by Gerard in 1956 and was subsequently transferred to Belgium and France. It was used in North America and Europe as a panacea. Chinese believed that it was also used to hallucinate or "see spirits." *A. calamus* was used as breath freshener, room refresher, insect repellant, and American tribes inhaled it to strive fatigue and hunger. The diseases and ailments it was used to cure are many. It was also used to bedeck houses both for aesthetic and magic purposes (Dobelis 1986; Ott 1975). Sweet flag was soon cultivated by numerous civilizations right through both the hemispheres.

17.1.4 Traditional Medicinal Uses

The rhizome of *A. calamus* has been found to possess numerous medicinal uses in the school of Ayurvedic medicine. The rhizome of *A. calamus* has anthelmintic, aphrodisiac, carminative, antispasmodic, diuretic, laxative, emetic, expectorant, bitter tonic, stimulant, and aromatic properties (Mukherjee et al. 2007a; b). It is also employed in the therapy of many diseases such as mental disorders (like schizophrenia), epilepsy, and memory disorders. Rhizome is also employed in the therapy of long-term diarrhea and dysentery, bronchial catarrh, fever, colic, cough (Rao 1983), asthma, as well as abdominal and glandular tumors (Kirtikar and Basu 1935). The skin of rhizome is said to have hemostatic property (Mukherjee et al. 2007a, b). The roots of *A. calamus* are used as antipyretic and antitussive (Dobriyal et al. 1997). The granulate form of sweet flag brings about the emesis when administered with the warm salt water (Imam et al. 2013). In powders, balms, enemas, pills, and even also in ghee preparations, rhizomes of *A. calamus* are used

(Kirtikar and Basu 2001). *A. calamus* also helps in removing excessive fats from the body (Rajput et al. 2014).

17.2 Pharmacological Actions

17.2.1 Antispasmodic Activity

The antispasmodic activity was found in the oil of *A. calamus* rhizome. The oil extracted from the rhizome of *A. calamus* obstructed the peristalsis of the intestines in rabbits and dogs by exhibiting its effect on the involuntary muscle tissue (Chopra et al. 1954). Several experiments were performed like lung perfusion and isolated tracheal chain experiments in which volatile oil was detected to be of better therapeutic use than alcohol and aqueous extract (Bose et al. 1960). Against various spasmogens, α-asarone and its volatile oil exhibited antispasmodic and relaxant effect. On extracted guinea pig ileum and analgesic activity in mice, hypothermia, and overall behavioral effect, the ethanolic extract of rhizome showed antispasmodic activity (Bhakuni et al. 1988). Antispasmodic activity was also detected in the raw extricate of *A. calamus*. The raw extricate of *A. calamus* induced obstruction of impulsive and high K^+ (80 mM) and caused contractions with respective EC_{50} values of 0.13 ± 0.04 and 0.42 ± 0.06 mg/mL, thus showing spasmolytic property, moderated possibly through calcium channel blockade (CCB) in the isolated rabbit jejunum preparations (Gilani et al. 2006).

17.2.2 Anthelmintic Activity

In vitro anthelmintic activity against the *Ascaris lumbricoides* was shown by the alcohol extract of *A. calamus* (Kaleysa Raj 1974). The exposure with the volatile oil of *A. calamus* within the time limit of 5 min revealed that the immensity of the periodic contractions of *Ascaris lumbricoides* was inhibited. Complete paralysis was caused within 25 and 5 min respectively when the phenolic and nonphenolic fractions of the oil were examined independently (Chaudhari et al. 1981). Another study states that the essential oil was also effective against *Meloidogyne incognita* (Singh et al. 1991). Within the range of 5–11 years of age, an interventional study was performed on about 147 children having roundworm infestation by Sharma et al. (1985). *A. calamus* powder weighing 250 g was administered thrice daily for 3 days. When the outcome was evaluated, it showed that in 17% no change was seen, while 83% were completely cured.

17.2.3 CNS Depressant Activity

Tripathi and Singh (1995) carried out a clinical trial of 50 cases of depression at OPD of Sir Sunderlal (SS) Hospital at Banaras Hindu University (BHU), Varanasi. The

patients were administered 500 mg *A. calamus* in a dose of two tablets, thrice a day, after meal with water. It showed a great depression and better rehabilitation when given for 6 weeks. The notable enhancement in evaluation is established on grading of manifestation on Hamilton depression grading scale. The apprise of enhancement before and after therapy was remarkable. Impulsive electrical property and monoamine levels of the brain were studied in the ethanolic extract of *A. calamus*. There was an elevation in the α activity with an elevation in the norepinephrine level in the cerebral cortex when rats were given the dose of *A. calamus*, but in midbrain and cerebellum levels were decreased when electrogram recording was revealed. In the same way, in caudate nucleus and midbrain increased levels of dopamine were recorded but decreased in the cerebellum. In different brain regions, *A. calamus* showed depressive actions by altering brain monoamine levels and by changing electrical activity (Hazra and Guha 2003).

17.2.4 Antidiarrheal Activity

According to the study, when mice were given the aqueous and methanolic decoction of *A. calamus* rhizome, there was a decrease in the total number of excreta, number of wet excreta, and total weight of excreta. Against the castor oil–induced diarrhea, methanolic decoction was more successful than aqueous plant derivative. Induction time of diarrhea and total weight of excreta were decreased notably by the methanolic extract of AC (Shoba and Thomas 2001). The result obtained establishes the effectiveness of these plant extracts as antidiarrheal agents.

17.2.5 Action on Respiratory System

The crude extricate of *A. calamus* has been found to be very effective for the respiratory ailments caused by the presence of peculiar association of airways-relaxant elements such as papaverine-like duplex obstruction of calcium channels and phosphodiesterase in the hexane fraction (Shah and Gilani 2010) and anticholinergic, rolipram—like phosphodiesterace-4 inhibitor in the ethyl acetate fraction (Jabbar and Hassan 2010). In patients having moderate to severe bronchial asthma, a clinical trial was done for 2–4 weeks in which the patients had to chew the fresh rhizomes of *A. calamus*. The anti-asthmatic potential was discovered in the rhizome of *A. calamus* without any aftereffects (Rajasekharan and Srivastava 1977). The noticeable or major effect was observed when small pieces of rhizome were given to asthmatic patients in curing of bronchospasm without any aftereffects (Chandra 1980).

17.2.6 Action on Cardiovascular System (CVS)

Essential oil of *A. calamus* has been studied for its activities of decreasing blood pressure (Chopra et al. 1954). After two-stage coronary ligation in dogs, the essential

oil of *A. calamus* showed the activity like quinidine which is the isomer of quinine to tackle atrial fibrillation, atrial flutter, and ventricular arrhythmias. It qualitatively resembled quinidine in isolated rabbit auricles as it extended conduction time and refractory period (Madan et al. 1960). Also, 50% alcohol extricate of *A. calamus* exhibited a dose-dependent hypotensive action on dog blood pressure (Moholkar et al. 1975). Antiarrhythmic properties and negative inotropic were also reported in its essential oil. Hypotensive activity was reported in anesthetized dogs and on frog heart perfusion experiments. β-Asarone revealed cardiac depressant activity (Arora 1965; Mamgain and Singh 1994). A total of 45 patients suffering from ischemic heart disease were shortlisted for a clinical trial from the OPD of SS Hospital, BHU. When the various groups were treated with the *A. calamus* extracts, they showed the remarkable improvements in the treatment of various diseases like dyspnea, chest pain, decreasing serum cholesterol level, decreasing serum low-density lipoproteins (LDL), increasing serum high-density lipoproteins (HDL), and improving ECG.

17.2.7 Anticonvulsant Activity

The methanol extricate of *A. calamus* manifested anticonvulsant property, at the doses of 100 and 200 mg/kg, successfully by potentiating the effect of gamma-aminobutyric acid (GABA) pathway in the nervous system (Jayaraman et al. 2010). The purified rhizome whose purification is done by boiling it in cow's urine as recommended in the *Ayurvedic Pharmacopeia of India* (API) before its curative use was analyzed in a maximal electroshock (MES) seizure model and the standard drug used was phenytoin. The crude rhizome of *A. calamus* exhibited eminent anticonvulsant activity in rats by reducing the interval of the tonic extensor while the processed rhizome when it was raw showed better therapeutic activity (Bhat et al. 2012). Antiepileptic property has also been reported in the oil of the *A. calamus* isolated from its rhizome. It was tested in adult albino mice where it efficiently restrained seizures in maximal electroshock seizure (MES) test (Khare and Sharma 1982).

17.2.8 Anticancer Activity

By affinity chromatography, two lectins were purified from the two species of AC which showed potent antimitogenic activity toward lymphocytes of human and mouse splenocytes. The two lectins which were purified showed the inhibitory action to some extent on a B-cell lymphoma,WEHI-279, and notably obstructed the magnification of murine macrophage cancer cell line, that is J774 (Bains et al. 2005). According to studies, β-asarone found in calamus oil also attributed to the anticancer activity (Palani et al. 2010). The inhibited proliferation induced by mitogen phytohemagglutinins was concluded from examining the ethanolic extract of AC rhizome which showed the in vitro anticellular activity of the ethanolic extricate. AC extract inhibited production of tumor necrosis factor-α, nitric oxide,

interleukin-2, and spreading of various cell lines of mouse and human origin (Mehrotra et al. 2003).

17.2.9 Antibacterial Activity

The antibacterial property of *A. calamus* was detected in its leaf and rhizome part. When the methanolic solution of *A. calamus* was taken, it showed strong antibacterial property toward the bacterial strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *and Klebsiella pneumonia* (Pokharel et al. n. d.). β-Asarone compound obtained from the third fraction of the raw methanolic solution of *A. calamus* has been revealed to have the highest inhibition toward *S. aureus*, *E.coli* strain at various concentrations (Manikandan et al. 2010). By an extract of rhizome, growth of gram-negative bacteria was significantly inhibited. *B. subtilis* and *Mycobacterium* spp. were easily vulnerable to calamus oil (Radušene et al. 2007).

17.2.10 Antifungal Activity

From the raw methanolic extract of *A. calamus* rhizome the β-asarone compound obtained was primarily responsible for the fungi toxicity (Saxena et al. 1990). β-Asarone possessed antifungal property in opposition to the yeast strain of *Saccharomyces cerevisiae*, *Cryptococcus neoformans*, *and Candida albicans* (Singh et al. 2011a, b). In the alcoholic extract of *A. calamus*, antifungal effect was studied toward the *Penicillium selenium, Aspergillus niger*, and yeast *Saccharomyces* (Vashi and Patel 1987).

17.2.11 Antiviral Activity

Alcoholic extract of the rhizome of *A. calamus* showed remarkable results in case of the Herpes simplex virus HSV-1 and HSV-2 respectively (Badam 1995).

17.2.12 Anti-HIV Activity

It was observed that the rhizome of *A. calamus* showed obstruction toward HIV-1 reverse transcriptase. In addition, 50% inhibitory concentrations (IC50) were reported to be the efficacy of the anti-HIV-1RT activity. This showed that the hexane crude extracts of *A. calamus* contained potent activity against HIV-1RT (Silprasit et al. 2011).

17.2.13 Antipyretic Activity

Methanolic extract and aqueous dichloromethane of *A. calamus* were tested for antipyretic activity. The dichloromethane and methanol extract reduced pyrexia. The activity was dependent upon time and concentration. The results exhibit the use of *A. calamus* in traditional medicine and contain the constituent which can be used as an antipyretic (Nethengwe et al. 2012).

17.2.14 Analgesic Activity

Analgesic activity at a dose of 500 and 250 mg/kg body weight was tested toward the methanolic extricate of *Oroxylum indicum* and *A. calamus*. At a dose of 25 mg/kg this was also tested toward the standard drug named diclofenac sodium. Assessed by acetic acid-induced writhing method, five adult Swiss albino mice were taken for study. Inhibited writhing reflex of methanolic extract of *A. calamus* was seen at the dose of 250 and 500 mg/kg body weight by 30.77 and 39.86%. So, the outcome of the current article indicated that the methanol extract of *A. calamus* roots possess analgesic activity on mice (Hosen et al. 2011).

17.2.15 Sedative Activity

The volatile oils of the *A. calamus* enhance the sedative activity of pentobarbitone in mice. The active constituent accountable for this activity is found in the various fractions of the oil which were either hydrocarbon fraction or an oxygenated fraction (Dandiya et al. 1959; Mukherjee et al. 2007a; b). With ethanol, hexobarbital, pentobarbital, and the steam volatile fraction in mice prolonged the sleeping time (Mukherjee et al. 2007a, b). In the volatile fraction of the petroleum ether extricate, the highest sedative property was recorded (Dandiya and Cullumbine 1959).

17.2.16 Antioxidant Activity

Antioxidant property was found in the rhizome of *A. calamus* and the compounds mainly responsible for this activity were the phenolic compounds. This property was examined by radical scavenging assay 2,2-diphenyl-1-picrylhydrazyl (DPPH) (Ahmed et al. 2009). The in vitro antioxidant activity by DPPH is dose concentration dependent and at the three different concentrations (0.01, 0.1, and 0.2 g/mL) DPPH scavenging property was reported and the maximum activity was recorded at the concentration of 0.2 g/mL (Govindarajan et al. 2003). The antioxidant activity was also reported by superoxide radical scavenging assay, nitric oxide scavenging assay, ferrous chelating assay, phosphomolybdenum assay and reducing power assay. In the acetone extricate, maximum antioxidant effect was seen followed by the aceto-nitrile and methanol, while the aqueous extract was dose dependent and possessed poor antioxidant activity (Bahukhandi et al. 2013). Aqueous extract showed

maximum antioxidant effects in metal ion chelation, lipid peroxidation (LPO), and DPPH assay (Karthiga et al. 2016; Manju et al. 2013). Thus, the outcome portrayed that *A. calamus* extracts possessed metal chelating activity, free radical scavenging property, and reducing power.

17.2.17 Antidiabetic Activity

A. calamus has the ability to be employed in the therapy of diabetes (Wu et al. 2009). The ethyl acetate of *A. calamus* was assessed in the streptozotocin (STZ)-induced and diabetic (db/db) mouse, the diabetic effect was evaluated from this. From the radix of the *A. calamus*, four fractions were obtained which showed a noticeable reduction in the blood glucose levels, low concentration of the lipids in the blood, and other effects by the insulin-sensitizing mechanism, and hence the *A. calamus* can be used in the treatment of diabetes (Kedar n.d.).

17.2.18 Insecticidal Activity

When the essential oil of the *A. calamus* was tested against the houseflies *Musa domestica*, it showed the insecticidal activity (Singh and Mehta 1998). Against the housefly *Musca nebulo* and *Culex fatigans* the solvents extract of the *A. calamus* rhizome were found to be toxic. Against the bugs, lice, and moths, powdered form of *A. calamus* rhizome was found to be effective (Subrahmanyam 1949); repellant property was also found against *Callosobruchus chinensis*, which is a plant beetle (Khan 1986). The inhibition of the interstitial property of the *Dysdercus koenigii* which is the instar larvae was found in the oil of *A. calamus*. The chemical constituent found in the *A. calamus* β-asarone formed a novel kind of antigonadal agent because of its antigonadal function which may be a novel and secure procedure toward the insect restrain (Saxena et al. 1977). When essential oil was employed as emulsified foliage sprays against the third instar larvae of *Spodoptera litura*, antifeedant and growth inhibitory effects were observed (Koul 1987) and also used in managing the stored grain insect *Spodoptera* (Agarwal et al. 1973). Sterility in the male houseflies was observed when the oil vapors of *A. calamus* were used. It showed the morphological change in the ovaries of *Thermobia domestica* (Saxena and Rohdendorf 1974; Mathur and Saxena 1975) (Figs. 17.3 and 17.4).

17.3 Phytochemistry

Phytochemical studies of *A. calamus* have reported the presence of phenylpropanoids, sesquiterpenoids, monoterpenes, xanthone glycosides, triterpenoid saponins, alkaloids, triterpene glycosides, steroids/sterols, amino acids, and fatty acids (Table 17.1). Sections 17.3–17.3.8 exhibit the chemical structures of the compounds

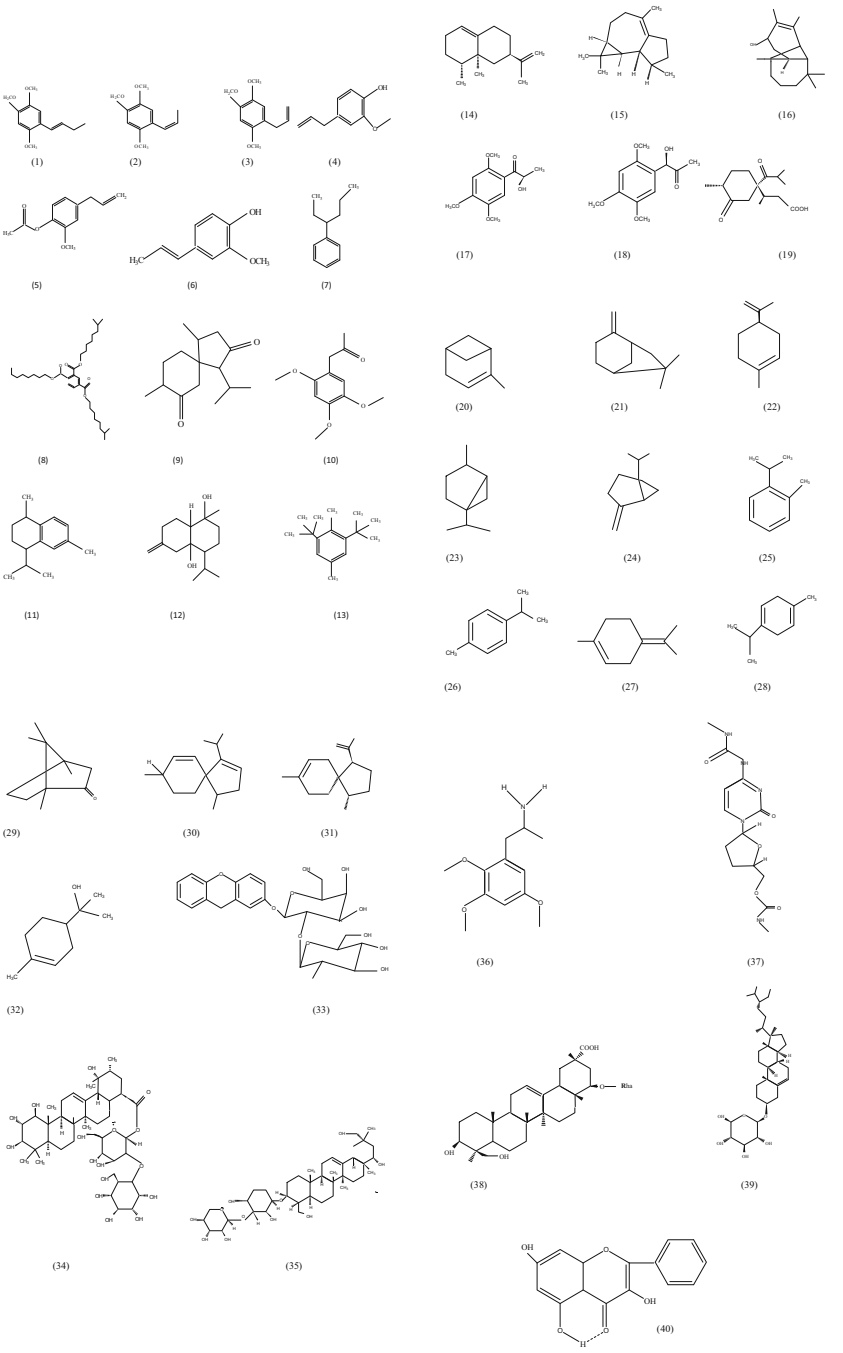

Fig. 17.4 Chemical structures of the major chemical constituents of *Acorus calamus*

Table 17.1 Different phytochemicals of *Acorus calamus*

Classification	Compound no.	Chemical ingredient	Parts/extract	References
Phenylpropanoids	1	α-Asarone	Rhizome/n-hexane, aqueous, methanol, ethanol	Mukherjee (2002), Nigam et al. (1990), Kumar et al. (2010), Lee et al. (2011), Padalia et al. (2014)
	2	β-Asarone		
	3	γ-Asarone		
	4	Eugenol	Rhizomes aqueous extract	Mukherjee (2002), Nigam et al. (1990), Kumar et al. (2015)
	5	Eugenyl acetate		
	6	Isoeugenol		
	7	Calamol	Rhizome aqueous	Patra and Mitra (1981)
	8	Acorin	Rhizome/chloroform	
Sesquiterpenoids	9	Acorone	Rhizome Hydro alcoholic	Zaugg et al. (2011)
	10	Acoramone	Rhizome/aqueous	Yao et al. (2018)
	11	Calamene		Mukherjee (2002), Nigam et al. (1990), Kumar et al. (2015)
	12	Calamenenol		
	13	Calameone		
	14	Valencene		Ozcan et al. (2002)
	15	Viridiflorene		
	16	Vulgarol B		Haghighi et al. (2017)
	17	Tatarinoid A	Rhizome/95% alcohol	Yao et al. (2018)
	18	Tatarinoid B		
	19	Acoric acid	Rhizome/ethanol	Li et al. (2017)
Monoterpenes	20	α-Pinene	Rhizomes, roots Aqueous	Mukherjee (2002), Nigam et al. (1990), Kumar et al. (2015), Ozcan et al. (2002)
	21	β-Pinene		
	22	Limonene	Roots (aqueous) Leaves	Ozcan et al. (2002), Haghighi et al. (2017)
	23	Thujane		Raja et al. (2009)
	24	Sabinene		Ozcan et al. (2002)

	25	o-Cymol		Haghighi et al. (2017)
	26	p-Cymene		Lee et al. (2011), Ozcan et al. (2002), Haghighi et al. (2017)
	27	α-Terpinene		Haghighi et al. (2017)
	28	γ-Terpinene	Rhizomes, roots Aqueous	
	29	Camphor	Rhizome, roots, leaves, /aqueous, hexane	Ozcan et al. (2002), Radusviene et al. (2007)
	30	α-Acoradiene	Roots aqueous	Ozcan et al. (2002)
	31	β-Acoradiene		
	32	α-Terpineol		
Xanthone glycosides	33	4,5,8-Trimethoxy-xanthone-2-O-β-D-glucopyranosyl (1–2)-O-β-D-galactopyranoside	Rhizome/ethanol	Rai et al. (1999)
Triterpenoid saponins	34	1β,2α,3β,19α-Tetrahydroxyurs-12-en-28-oic acid-28-O-{(β-D-glucopyranosyl (1–2)}-β-D galactopyranoside	Rhizome/ethanol	Rai et al. (1998)
	35	3-β,22-α-24, 29-Tetrahydroxolean-12-en-3-O-{(β-Darabinosyl (1,3)}-β-D-arabinopyranoside		
Alkaloids	36	Trimethoxyamphetamine, 2,3,5 and Pyrimidin-2-one	Rhizome/ethanol	Kumar et al. (2010)
	37	4-[N-methylureidol]-1-[4methylamino carbonyloxy methyl]		
Triterpene glycosides	38	22-[(6-deoxy-α-L-rhamnopyranosyl) oxy]-3, 23-dihydroxy-, methyl ester (3β, 4β, 20α, 22β)	Root, rhizome/ethyl ether	Wu et al. (2007)
Steroids/sterols	39	β-Daucosterol		Wu et al. (2007)
Flavones	40	5,7-Dihydroxyflavanol		Stahl and Keller (1981)

from *A. calamus*. The Chemical structures of the major chemical constituents of *Acorus Calamus as shown in* Fig. 17.4

17.3.1 Phenylpropanoids

A number of phenylpropanoids have been extracted from the plant. Some of the phenylpropanoids extracted are α-asarone(1), β-asarone (2), γ-asarone (3) (Mukherjee 2002; Nigam et al. 1990), eugenol (4), eugenyl acetate (5), isoeugenol (6) (Kumar et al. 2015; Mukherjee 2002; Nigam et al. 1990), calamol (7), acorin (8) (Padalia et al. 2014).

17.3.2 Sesquiterpenoids

Phytochemical study revealed the number of sesquiterpenoids in the plant such as acorone (9) (Zaugg et al. 2011), acoramone (10) (Yao et al. 2018), calamene (11), calameone (12), calamenenol (13) (Kumar et al. 2015; Mukherjee 2002; Nigam et al. 1990), valencene (14), viridiflorene (15) (Özcan et al. 2002), vulgarol B (16) (Haghighi et al. 2017), tatarinoids A & B (17, 18) (Li et al. 2017), acoric acid (19) (Yao et al. 2018).

17.3.3 Monoterpene

Reported monoterpenes in the plant are α-pinene (20), β-pinene (21) (Kumar et al. 2015; Mukherjee 2002; Nigam et al. 1990; Özcan et al. 2002), limonene (22) (Haghighi et al. 2017; Özcan et al. 2002), thujane (23) (Raja et al. 2009), sabinene (24) (Özcan et al. 2002), O-cymol (25) (Haghighi et al. 2017), p-cymol (26) (Haghighi et al. 2017; Lee et al. 2011; Özcan et al. 2002), α-terpinene (27), γ-terpinene (28) (Haghighi et al. 2017), camphor (29) (Özcan et al. 2002; Radušienė et al. 2007), α-acoradiene (30), β-acoradiene (31), α-terpineol (32) (Özcan et al. 2002).

17.3.4 Xanthone Glycosides

4,5,8-Trimethoxy-xanthone-2-O-β-D-glucopyranosyl (1–2)-O-β-D-galactopyranoside was newly reported from the plant (33) (Rai et al. 1999).

17.3.5 Triterpenoid Saponins

The compounds belonging to this category are 1β, 2α, 3β, 19α-Tetrahydroxyurs-12-en-28-oic acid-28-O-{(β-D-glucopyranosyl (1–2)}-β-D galactopyranoside (34) and

3-β,22-α-24, 29-Tetrahydroxolean-12-en-3-O-{(β-D-arabinosyl (1,3)}-β-D-arabinopyranoside (35) (Rai et al. 1998).

17.3.6 Alkaloids

Alkaloids reported from the plant are trimethoxyamphetamine, 2,3,5 (36) and pyrimidin-2-one, 4-[N-methylureidol]-1-[4methylamino carbonyloxy methyl] (37) (Kumar et al. 2010).

17.3.7 Triterpene Glycoside

22-[(6-Deoxy-α-L-rhamnopyranosyl)oxy]-3, 23-dihydroxy-, methyl ester, (3β, 4β, 20α, 22β)(38) is the reported triterpene glycoside from the *A. calamus* (Wu et al. 2007).

17.3.8 Steroids/Sterols

β-Daucosterol (39) (Wu et al. 2007) is reported from the plant.

17.3.9 Flavones

5,7-Dihydroxyflavanol(40) (Galangin) is extracted constituent isolated from the *A. calamus* (Stahl and Keller 1981).

17.4 Conclusion

In the current review, we have made an effort to survey and contribute the utmost information of pharmacognostical with history and geographical distribution, traditional claims, phytochemical and pharmacological information of *A. calamus*, a remedial herb employed in the Indian school of medicine. Study of literature displayed the presence of triterpenoid, sesquiterpenoids, alkaloids, steroids, and glycosides in various parts of this plant were discovered. *A. calamus* showed the blood pressure lowering/vasomodulator activity with other important activities. The plant showed anticonvulsant, antipyretic, analgesic, antitussive, and antitumor activities. Increased blood pressure and tumor asserts millions of lives every calendar year on worldwide basis which is predominantly due to proliferated resistance to preexisting drugs. In spite of the fact that drugs presently in use for the treatment of the same were initially extracted from the plants, further search for extraction and recognition of new drugs is need of time. The plant has strong antitumor and vasomodulator claims and may lead to antitumor and vasomodulator compounds.

The ethnopharmacological procedure employed in exploring the new drugs for such compounds from such plants emerges to be pleasant in comparison to the arbitrary testing procedure. However, a favorable procedure is required to employ these agents as model for plotting new derivatives with improved properties. This review will undoubtedly will come to the aid for the researchers and practitioners, handling with this plant, to know its nature and properties. Due to its indispensable value, at last it is not incorrect to portray that this plant is magnificent conventional plant.

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