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

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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).

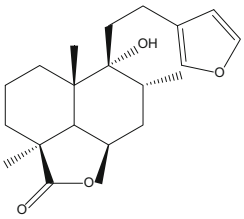
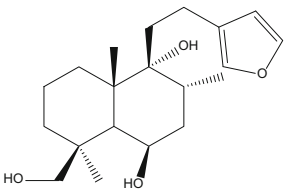
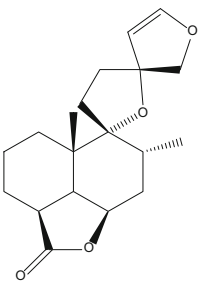
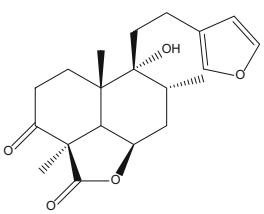
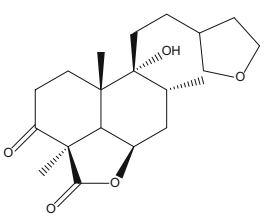
11.5 Phytochemistry of *M. vulgare*

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

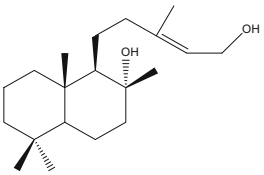
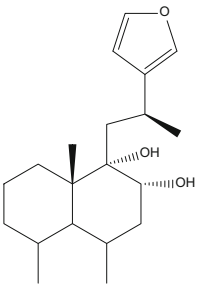
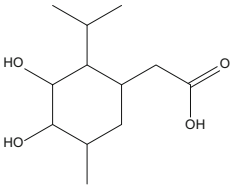
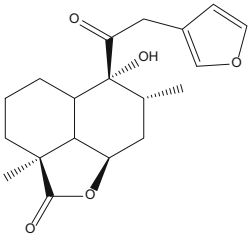
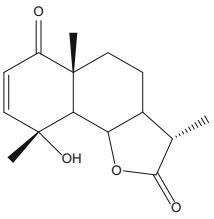
Diterpenoids constitute the large group of constituents present in aerial parts of *M. vulgare* (Piozzi et al. 2006). There are nine distinct kinds of diterpenes along with their alcoholic derivatives which have been recognized and isolated from *M. vulgare* (Rodrigues et al. 1998). Marrubiin is a diterpenoid 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)

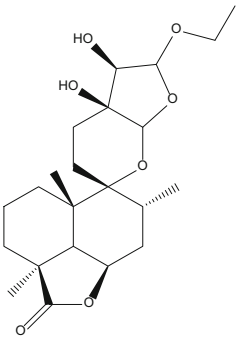
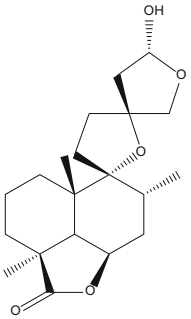
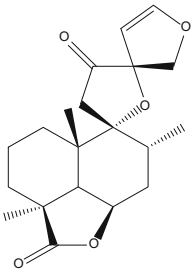
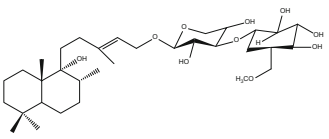
(continued)

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)

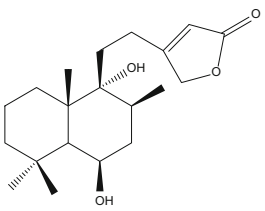
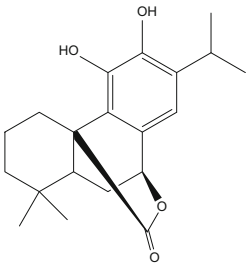
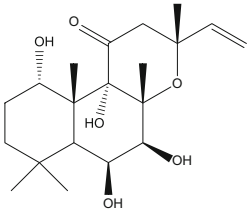
(continued)

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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