A Taxonomical, Morphological and Pharmacological Review of *Marrubium vulgare* L., An Old Medicinal Plant in Iran

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Abstract

***Marrubium vulgare* L. (common name: Horehound, hoarhound) is one of the medicinal plants which has been used in the treatment of stomach, arrhythmia, asthma, jaundice, lung diseases and liver disorders in Iranian traditional medicine. Other properties are expectorant, antispasmodic, tonic, anti-infective agent and externally, it has been used in ulcers and wounds. Flowers in *M. vulgare* generally appear in early spring and regularly visited by readily nectar gathering bees. The plant is a good candidate for phytoremediation of Hg contaminated soils. Previous phytochemical studies showed the presence of alkaloids, lactones, steroids, flavonoids, tannins, phenylpropanoid esters, and diterpenoids in *M. vulgare.* In this review we focused on the several aspects of taxonomy, morphology, chemical composition and traditional medicine of horehound.**

Keywords: **Ethnobotany, *Marrubium vulgare*, Medicinal plant, Phytochemistry, Taxonomy**

Introduction

The Lamiaceae Martinov (=Labiatae Adans., the mint family) has a word-wide distribution with more than 7200 species across approximately 240 genera [1]. The genus *Marrubium* (Lamiaceae) is comprised of about 49 accepted species.

Some of the species within *Marrubium* such as *M. vulgare* are used as medicinal plant traditionally [2]. *M. vulgare* L. (horehound) has been known as a native species for Asia, Europe and north of Africa [2, 3]. Horehound has been used as an expectorant cough remedy since ancient Egyptian times. Its name comes from the word hoary, due to the white hairs that cover horehound leaves, and hound, because it was used in ancient Greek medicine to treat bites from rabid dogs. Horehound is used in Indian Ayurvedic medicine to treat acute or chronic bronchitis and whooping cough. In Germany, horehound is used to treat dyspeptic complaints such as feeling of repletion, flatulence and loss of appetite. It is also used for catarrh of the respiratory tract as a component of some antitussive and expectorant drugs. It is a common expectorant component of European made herbal cough remedies [4]. In a survey, an aqueous extract of *M. vulgare* showed anti-diabetic activity and effects on body weight properties [5]. The major chemical components of *M.vulgare* are β- Cariophyllene (11 to 32%), Germacerene-D (9 to 20%), β-Bisabolene (25%), (E)-β-Farnesene (8 to 11%), Carvacrol (14%), β-Citronellol (8-9%), E-Caryophyllene (25%), δ-Amorphene (10%), γ-Eudesmol (11%).

Taxonomy

Plant name

Horehound, hoarhound is the most well-known English common name for this genus and common white horehound is English name for *M. vulgare* in all of the distribution areas in the world and is a synonym name of *M. ballotoides* Boiss. & Bal. [6, 7, 8, 9, 10]. It is known with other regional names in different parts of the world such as:

Persian= Faracion, Ghandnaye kohi, Shenar, Oftan-Sar, Korar [7, 9, 10, 11].

Grecian= Faracin, Berson [11].

Romanic= Madroptim [11].

Indian= Faracim, Shafar, shevir [10].

Arabic= Hashish el Kalb, Algama, Sogafol-Arz, Sharir [9, 10, 11, 12].

French: Marrube blanc [13].

Germany: Mauerandron, Weisse andorn, Andorn [13].

Botany

The genus *Marrubium* L. belongs to Lamioideae subfamily. In the plant list data base (http://www.theplantlist.org) there are 120 scientific plant names of species rank for the genus *Marrubium*, of these 49 are accepted species names. The genus is distributed in temperate regions of Europe, North Africa and Asia to western China with a few species naturalized in North and South America [14]. Many species of the Lamiaceae family are considered of high importance because of their uses in medicine, culinary, and cosmetics [15]. *Marrubium* is present in Iran with 11 species from which only one is endemic (*M. procerum*

Bunge) [16, 17]. Most *Marrubium* species are distributed in steppes, arid and semiarid areas of Iran. ***M. vulgare*** L. is a perennial subshrub, C3, herbaceous plant, reproduces by seeds and 2n = 34 [3, 18].

Morphology

Herbaceous, erect and ascending, perennial subshrub with stem bases becoming sublignescent; stems usually branched to form a rounded bushy plant; up to 100 cm tall, 20-100 cm wide. A tough, woody, branched taproot or having numerous fibrous lateral roots. Stems have 20-100 cm tall, are quadrangular except in old sublignescent growth. Leaves arranged opposite along stem, decussate. Leaf blades broadly ovate, oval, suborbicular, or subreniform; 1-4 cm or up to 6 cm long, 1-5 cm wide, acute to rounded or truncate at apex, acute to cordate at base, strongly corrugate and rugose, margins crenate to dentate, pubescent above, gray-green above, cinereous-lanate beneath, veins prominent on lower surface; lower leaves on pedicels equaling blade or shorter, upper leaves subsessile. Inflorescence in axils of upper leaves; flowers sessile and crowded in dense whorls, these axillary subglobose multi-flowered verticals forming interrupted spikes along stem; often subtended by leaves. Calyx is tubular, 3-6 mm long at anthesis, larger in fruit, 5-10 veined; short soft-hairy, 10-toothed, each tooth with a small hooked spine/bristle, recurved at maturity, alternately long and short; calyx spreading at maturity. Corolla is white to pale lavender, tubular, bilabiate, small, 5-10 mm long, tube about 2-4 mm longer than calyx; 2-lipped, upper lip erect, medially notched, laterally reflexed, lower lip spreading, 3-lobed with middle lobe larger. Flowers are arranged perfect. Style included in corolla tube. Stamens are arranged in 4, didynamous, lower pair usually larger; anther sacs divergent; included in corolla tube. Seeds are 4-parted, seed-like nutlets; each nutlet 1-seeded, ovoid to oblong, 1-2 mm long, somewhat 3-angled, obtuse or truncate at apex, somewhat reticulate-roughened, brown to black [3].

Trichomes

Trichomes are one of the most important characters for identification of the genera and species in taxonomic studies in Lamiaceae [19, 20, 21, 22, 23, 24]. Trichomes show a range of variation within the family. Simple glandular and non- glandular as well as peltate are the most common types of trichomes, but stellate and branched hairs are also characteristic of some genera. Stellate and branched hairs are rather common in subfamily Lamioideae and have been observed in many genera i. e. *Marrubium*, *Ballota*, *Stachys*, *Phlomis*, *Eremostachys* and *Lagochilus*. In Lamiaceae some genera are characterized by stellate trichomes, i. e. in *Marrubium* & *Lavandula*. Most of the long branches in stellate hairs are four celled in upper surface in populations of ***M. vulgare*** that with altitude increase the number of short branches are increased too (from 7 to 14). The effect of the ecological conditions i.e. arid areas and altitude are important factors for morphological variations and density of trichomes [14].

Anatomical characters

M. vulgare epidermis consists of one layer of large cells. Type of stomata is anomocytic on adaxial surface. Isobilateral mesophyll includes 4-5 layers of long palisade cells adaxially and 1-2 layers of short cells on abaxial surface. Vascular bundles are collateral and surrounded by parenchymatous bundle sheaths [27].

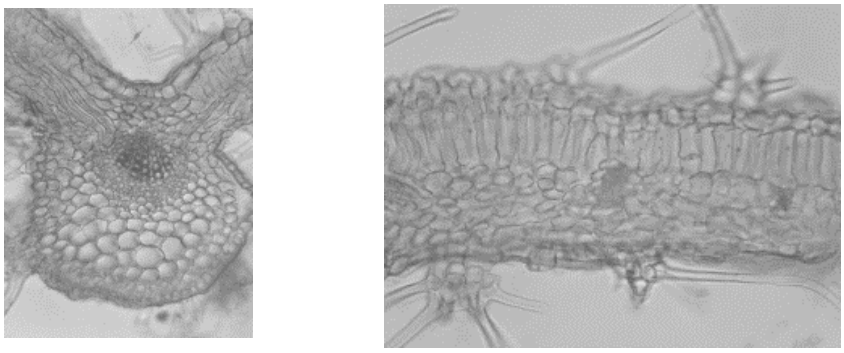

Figure 1- *M. vulgare* transversal section of leaf (details of mesophyll)

Figure 2- white horehound [https://ast.wikipedia.org/wiki/*Marrubium vulgare*]

Ecology

Origin

The genus Marrubium (Lamiaceae) is comprised of about forty species. *M. vulgare* is native to Asia (Afghanistan, Armenia, Azerbaijan, China (Xinjiang), Cyprus, Iran, Kazakhstan, Lebanon, Russian Federation (Ciscaucasia), Syria, Turkey, Turkmenistan, Uzbekistan into Pakistan), Europe (Albania, Austria, Belarus, Belgium, Bulgaria, Czechoslovakia, Denmark, Estonia, England, France including Corsica, Greece including Crete, Hungary, Italy including Sardinia and Sicily, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Russian Federation (southwest European areas), Spain including Baleares, south Sweden, Switzerland, Ukraine including Krym, Yugoslavia), and northern Africa (north Algeria, north Libya, Morocco, Azores, Madeira Islands, Canary Islands, Tunisia). This plant is being used since ancient as a medicinal plant [2, 3].

Hg absorption from environment

Mercury (Hg) is an environmental pollutant which is mainly supplied via anthropogenic sources to the soil. It is harmful because of its toxicity, mobility, bioaccumulation, methylation process and transport in the atmosphere [26]. Recent studies have shown that *M. vulgare* can absorb high Hg from soil. Moreno-Jimenez et al. have shown the plant has a high resistance to Hg and is able to extract around 10–30 g Hg ha^{-1} $year^{-1}$ in aerial parts, so can be a good candidate for Hg phytoremediation of contaminated soils [27].

Cultivation

Seeds from a specific location seem to have location-dependent germination requirements, with dormancy differing across continents, and even between populations. After collection of the mature *M. vulgare* seeds in October, germination rate was less than 35% at trial temperatures between 10-30°C, with the majority of germination occurring between 1826°C. Following 1 month of storage under 3 sets of conditions (26°C-dry, 0°C-dry, 0°C-moist), 78% germination occurred for the seeds which have been kept at 32°F-moist (0°C). It took 3 months of dry storage at 26°C for 80% germination to occur. Seeds stored under 0°C needed 4 months of storage to reach 80% germination. Some studies have shown that germination rates of un-stratified seeds were highest when temperatures fluctuated at least 15°C diurnally when tested at intervals over a year. Optimum temperature regimes of un-stratified seeds were 15/40°C and 20/40°C. It was also found that the seeds of *M. vulgare* are poor germinators at very cold temperatures in seedbeds. Cold and moist stratification for 4-8 weeks enhanced the germination rate over a wide range of temperatures, with lower germination rates if stratification period was shorter or longer as several responses to temperature regimes were observed between populations from differing locations. Crops grow appropriately in well-drained, neutral to alkaline soil in sun. *M. vulgare* generally flowers early in the spring, readily foraged by bees for the nectar. It has been reported that this plant also has the potential of self-fertilization, although there is a lack of adequate researches to identify the seeding potential by self-pollination. Plants are cut when are in flowering stage and used fresh or dried [3, 28].

Phytochemical components

M. vulgare and other species in Iran

Prior to the introduction of chemical medicines, man relied on the healing properties of medicinal plants [29]. The knowledge of herbal remedies in traditional cultures has contributed significantly to the development of the use of drugs derived from plants, considering their widespread use, with 80% of the world's population relying on such medicines for their health care [2]. The Phenolic acids, caffeic acid, and rosmarinic acid, are common constituents of the family Lamiaceae. Forty percent of the species of Lamiaceae family are thought to contain compounds that possess aromatic properties. Caffeic acid plays a central role in the biochemistry of this family. Previous phytochemical studies have also showed the presence of alkaloids, lactones, steroids, flavonoids, tannins, phenylpropanoid esters, vitamin C and diterpenoids in *M. vulgare* [2, 30, 31, 32, 33]. *Marrubium* is an important medicinal plant in Iranian medicine with 10 species. The genus is known to produce many diterpenoids such as marrubiina (Figure 3), identified in 1842, which was the first diterpenoid and major compound to be isolated and characterized from *M. vulgare* leaves. Marrubiin exists in high concentrations in many traditionally important Lamiaceae species and has demonstrated excellent pharmacological properties with high safety margins in different inflammation models [2, 30, 34]. Moreover, some studies demonstrated the considerable antioxidant activity of *M. vulgare* is associated with the presence of marrubiin along with phenolics and flavonoids exerting a synergistic effect [34]. Table 1 illustrates the main components (percentage up to 1%) of various species of *Marrubium*.

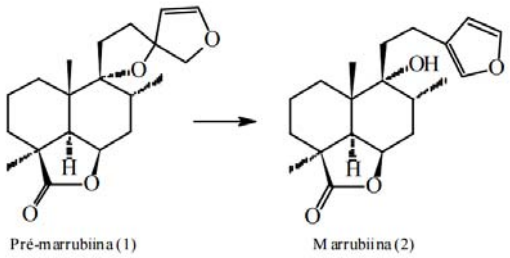

Figure 3-Conversion of pre-marrubiina to marrubiina [35]

There are several studies about the species components and their percentages that are related to several factors such as collection time, drying conditions, altitude, soil, climatic and geographic factors. The chemical compositions of *M. vulgare* essential oil from various origins have been the subject of many studies. For example the major constituents of *M. vulgare* essential oil grown in Egypt from the aerial parts were carvacrol, β- phellandrene and carvyl acetate with 36.28, 15.49, 11.52 percentage respectively [50]. While the major composition of the essential oil obtained from the dried flowering aerial parts of *M. vulgare* from Iran were β-bisabolene (20.4%), δ-cadinene (19.1%) and isocaryophyllene (14.1%). In Tunisia, the main constituents *of M. vulgare* essential oil were y-Eudesmol (11.93%), β-Citronellol (9.90%), Citronellyl formate (9.50%) and Germacrene-D (9.37%) [46]. From Poland E-Caryophyllene, Germacrene D, Carvacrol and δ-Amorphene were the main components of *M. vulgare* essential oil [42]. Germacrene D and Caryophyllene oxide are two dominant components of the oils obtained from other

Table 1- The main phytochemical components (%) of the essential oils of the aerial parts of different *Marrubium* species

Scientific name / Components	*M. anisodon*	*M. astracanicum*	*M. cuneatum*	*M. cordatum*	*M. crassidens*	*M. duabense*	*M. parviflorum*	*M. persicum*	*M. propinquum*	*M. vulgare*
Monoterpene hydrocarbon (MH)										
α-Pinene [5,39,41,43,44,47]	-	1.0	-	-		1.8, 1.2	-	1.9	1.8 4.6	-	0.8, 2.16, 6.64
α-Terpineol [45]	-	-	-	-	-	10.78	-	-	-	-	-
γ-Terpineol [43]	-	-	-	-	-	-	-	-	-	-	1.39
α-Thujone [46,47]	-	-	-	-	-	-	-	-	-	-	2.29, 2.45
1,8-Cineole [43,46,47]	-	-	-	-	-	-	-	-	-	-	3.72, 3.75,8.17
Camphene [47]	-	-	-	-	-	-	-	-	-	-	3.12
Camphor [47]	-	-	-	-	-	-	-	-	-	-	1.03
Carvacrol [18,44]	-	-	2.3	-	-	-	-	-	-	-	14.95
Citronella [2,36,37,38]	-	16.9	-	-	-	-	-	-	-	-	-
Eugenol [5,43]	-	-	-	-	-	-	-	-	-	-	1.3, 2.91
Geijerene [5]	-	-	-	-	-	-	2.3	-	-	-	-
Geraniol [47]	-	-	-	-	-	-	-	-	-	-	3.70
Geranyl formate [46,47]	-	-	-	-	-	-	-	-	-	-	6.25, 6.02
Limonene [5,41,42,44,45]	-	-	-	-	1.6	33.53	3.2	2.5	-	-	0.4, 1.53
Linalool [18]	-	-	1.6	-	-	-	-	-	-	-	-
Myrcene [44]	-	1.7	-	-	-	-	-	-	-	-	-
p-Cymene [43]	-	-	-	-	-	-	-	-	-	-	4.76
Piperitone [43]	-	-	-	-	-	-	-	-	-	-	2.11
Pregeijerene [44]	-	1.0	-	-	-	-	-	-	-	-	-
Sabinene [41]	-	-	-	-	-	-	-	1.3	-	-	-
Thymol [2,36,37,38]	-	10.6	-	-	-	-	-	-	-	-	-
trans-p-Menth-2-en-1-ol [45]	-	-	-	-	-	1.08	-	-	-	-	-
trans-β- damascenone [44]	-	1.1	-	-	-	-	-	-	-	-	-
β –Citronellol [46]	-	-	-	-	-	-	-	-	-	-	9.90,8,
β- Pinene [5]	-	-	-	-	-	-	2.4	-	-	-	2.4
β-Ionone [43]	-	-	-	-	-	-	-	-	-	-	1.16
β-Thujene [50]	-	-	-	-	-	-	-	-	-	-	2.93
γ-Terpinene [42,43]	-	-	-	-	-	-	-	-	-	-	1.75, 2.62
Diterpene alcohol (DO)										
Isophytol [39,40]	6.095	-	4.024	-	-	-	-	-	5.552	-

Table 1- Continue

Scientific name / Components	*M. anisodon*	*M. astracanicum*	*M. cuneatum*	*M. cordatum*	*M. crassidens*	*M. duabense*	*M. parviflorum*	*M. persicum*	*M. propinquum*	*M. vulgare*
Selareol [40]	-	-	2.266	-	-	-	-	-	-	-
Sesquiterpene hydrocarbon(SH)										
α- Bergamoten [44]	-	-		-	1.3	-	-	-	-	-
δ -Cadinene [5,44]	-	-	-	-	1.9	-	-	-	-	2.1
γ-Cadinene [5]	-	-	-	-	-	-	-	-	-	2.5
α-Copaene [5,44]	-	-	-	-	1.3	1.59	0.8	-	-	3.4
(E)- β-Farnesene [5,43]	-	-	-	-	-	-	2.0	-	-	8.3, 11.39
α-Humulene [2,36,37,38]	-	33.7	-	-	-	-	-	-	-	-
(Z)-β-Farnesene [42]	-	-	-	-	-	-	-	-	-	3.95
1-Selinene [40]	-	-	-	-	-	-	-	-	6.596	-
Bicycloelemene [40,44]	2.501	-	3.367	-	1.0	-	-	-	-	-
Bicyclogermacrene [2,39,40,41,44,45]	7.797	11.9	37.9, 10.82, 5.2	-	1.9, 14.2	6.01	14.640, 26.3	1.3	3.756	-
E-Nerolidol [42]	-	-	-	-	-	-	-	-	-	4.52
Germacrene- D [2,5,18,40,41,42,44,46,47]	5.569	23.4	24.1%, 7/708, 15.6	-	2.6, 14.2	-	10.434, 21.5	10.5	10.985, 15.8	9.7, 20.23, 10, 9.37, 10
Ledene [44,47]	-	-	-	-	2.9	-	-	-	-	5.15
β- Elemene [44]	-	-	-	-	1.6	-	-	-	-	-
β-Bisabolene [5,44]	-	-	-	-	2.1	-	-	-	-	25.4
β-bourbonene [40,42,44]	-	-	2.341	-	1.4	-	-	-	-	2.18, 1.80
β-Caryophyllene [2,5,18,36,37,38,39,41,43,49]	-	13.1	5.2	-	3.8	-	15.6	7.4	20.1	11.6, 32.19
β-Cubebene [43,47]	-	-	-	-	-	-	-	-	-	3.30, 1.08
β-Farnesene [2, 39,41]	-	-	-	-	1.5	-	-	-	-	-
β-Sesquiphellandrene [40]	-	-	-	-	-	-	14.640	-	-	-
δ-Amorphene [42]	-	-	-	-	-	-	-	-	-	10.22
Oxygenated sesquiterpenene (SO)										
(+)-spathulenol [40]	2.745	-	7.051	-	-	-	9.117	-	3.678	-
1-Bisabolol [40,41]	2.064	-	-	-	-	-	-	1.7	-	-
Caryophyllene oxide [2,36,37,38,39,40,41,42,43,44,45]	2.247	35.8	3.048	-	3.4 , 4.6	1.00	2.811	2.1	3.174	2.33, 4.06
Cis-Nerolidol [5]	-	-	-	-	-	-	-	-	-	2.3

Table 1- Continue

Scientific name / Components	*M. anisodon*	*M. astracanicum*	*M. cuneatum*	*M. cordatum*	*M. crassidens*	*M. daubense*	*M. pariflorum*	*M. persicum*	*M. propinqum*	*M. vulgare*
epi-Globulol [45]	-	-	-	-	-	1.16	-	-	-	-
Farnesol [5]	-	-	-	-	-	-	-	-	-	4.3
Furan-2-one,4-phenyltetrahydro [47]	-	-	-	-	-	-	-	-	-	1.44
Globulol [44]	-	1.3	-	-	-	-	-	-	-	-
Nerolidol [40]	2.211	-	-	-	-	-	-	-	-	-
Spathulenol [2,36,37,38,44,45]	-	6.8	-	-	5.6	1.08	-	-	-	-
T-Cadinol [44]	-	-	-	-	1.0	-	-	-	-	-
T-Muurolol [44]	-	1.3	-	-	-	-	-	-	-	-
Viridiflorol [44]	-	1.1	-	-	-	-	-	-	-	-
α-Cadinol [42]	-	-	-	-	-	-	-	-	-	2.63
γ-Eudesmol [46,47]	-	-	-	-	-	-	-	-	-	11.93, 11
Non-terpenoids (NT)										
α-Tolualdehyde [41]	-	-	-	-	-	-	-	2.4	-	-
1,2-Benzendicarboxylic acid [44]	-	1.8	-	-	-	-	-	-	-	-
1-Octadecanol [40]	-	-	2.923	-	-	-	-	-	-	-
1-Octen-3-ol [39,45]	-	-	-	-	2.8	1.3	-	-	-	-
1-Tridecene [40]	3.348	-	-	-	-	-	-	-	-	-
2-Pentadecanol [40]	2.198	-	-	-	-	-	-	-	-	-
2-Pentadecanone [40]	-	-	-	-	-	-	1.991	-	-	-
2-Pentadecanone,6,10 [45]	-	-	-	-	-	1.74	-	-	-	-
3-Octanol [45]	-	-	-	-	-	3.32	-	6.1	43.8	-
4-Oxo-7-Isodamascol [40]	-	-	-	-	-	-	-	-	4.296	-
6,10,14-Trimethyl-2-Pentadecanone [40]	-	-	-	-	-	-	-	-	5.093	-
9,12-Octadecadienoic acid [40]	-	-	-	-	-	-	-	-	5.221	-
Acetophenone [41,48]	-	-	-	-	15.8	-	-	14.6	-	-
Artemisia acetate [40]	-	-	-	-	-	-	3.861	-	-	-
Citronellyl formate [46,47]	-	-	-	-	-	-	-	-	-	9.50,10
Cyclononasiloxane [47]	-	-	-	-	-	-	-	-	-	4.3
Docosane [39,40]	-	-	0.6	-	7.2	-	-	-		
Dodecanal [45]	-	-	-	-	-	2.53	-	-	-	-
Geranyl tiglate [47]	-	-	-	-	-	-	-	-	-	7.1
Heptanal [43]	-	-	-	-	-	-	-	-	-	4.26

Table 1- Continue

Scientific name / Components	*M. anisodon*	*M. astracanicum*	*M. cuneatum*	*M. cordatum*	*M. crassidens*	*M. duabense*	*M. parviflorum*	*M. persicum*	*M. propinqum*	*M. vulgare*
Hexa hydro farnesyl acetone [44]	-	1.0	-	-	-	-	-	-	-	-
Hexacosane [39]	-	-	-	-	2.0	-	-		-	-
Hexadecane [40,45]	2.284	-	-	-	-	0.94	-	-	-	-
Hexadecanoic acidb [5]	-	-	-	-	-	-	-	-	-	3.2
Hexahydrofarnesyl acetone [40,41]	-	-	1.9	-	-	-	-	2.9	-	-
Methylcyclopentane [2,36,37,38]	-	15.5	-	-	-	-	-	-	-	-
M-tolualdehyde [41,48]	-	-	-	-	23.3	-	-	19.1	-	-
Neryl acetate [47]	-	-	-	-	-	-	-	-	-	3.41
n-Heptane [2,36,37,38]	-	7.4	-	-	-	-	-	-	-	-
N-hexadecanol [40]	6.483	-	13.566	-	-	-	5.886	-	-	-
n-Nonane [39,41]	-	-	-	-	2.1	-	-	1.6	-	-
Nonacosane [39,41]	-	-	-	-	13.1	-	-	2.3	-	-
N-Trimethylsilyl trifluoroacetamide [46]	-	-	-	-	-	-	-	-	-	2.35
Octacosane [39,41]	-	-	-	-	1.9	-	-	1.1	-	-
Oleyl alcohol [40]	-	-	2.886	-	-	-	-	-	-	-
o-Tolualdehyde [41]	-	-	-	-	-	-	-	3.5	-	-
Oxygenated sesquiterpenene [2]	-	13.4	-	-	4.3	-	-	-	-	-
Palmitic acid [40,45]	-	-	-	-	-	4.13	-	-	14.425	-
Pentacosane [40]	4.821	-	2.380	-	-	-	-	-	-	-
Pentadecanol [40]	-	-	5.173	-	-	-	-	-	-	-
Pyrocatechol [2]	-	-	-	-	-	-	-	-	-	-
Sclareoloxide [40]	-	-	-	-	-	-	-	-	4.143	-
Sesquiterpene hydrocarbon [2]	-	72.3	-	-	11.9	-	-	-	-	-
Tetracosane [40]	-	-	3.470	-	-	-	-	-	-	-
Tetradecanal(45)	-	-	-	-	-	0.94	-	-	-	-
trans-chrysanthemal [40]	9.287	-	-	-	-	-	-	-	-	-
Tricyclene [5]	-	-	-	-	-	-	-	-	-	3.8
Tridecanedial [40]	2.223	-	-	-	-	-	-	-	-	-
Warburganal [40]	-	-	-	-	-	-	-	-	3.331	-
ρ-Methoxyacetophenone [18]	-	-	5.4	-	-	-	-	-	-	-
Geranyl linalool [43]	-	-	-	-	-	-	-	-	-	2.58
Benzyl benzoate [43]	-	-	-	-	-	-	-	-	-	1.08

plant species of the genus *Marrubium.* Comparison of different studies confirms that the differences in the volatile composition of the plants could be attributed to genetic (genus, species, and ecotype), chemotype, distinct environmental and climatic conditions, seasonal sampling periods, geographic origins, plant populations, vegetative plant phases, soil, climate, extraction and quantification methods [43].

Biological activity of *M. vulgare*

Marrubiin, a furane labdane diterpene, is the main analgesic compound present in *M. vulgare*. It was mentioned that Marrubiinic acid is a derivative component of Marribin, which exhibited significant analgesic effect against the writhing test in mice. In addition, Marrubiinic acid showed better activity and excellent yield, and its analgesic effect was confirmed in other experimental models of pain in mice. The results showed that Marrubiinic acid could be used as a model to obtain new and more potent analgesic drugs [51]. Many researchers have indicated the multifaceted therapeutic activities of *M. vulgare,* which some of them are given below.

Anti-diabetic activity

In a study, an aqueous extract of *M. vulgare* showed anti-diabetic activity and effects on body weight properties [52]. In another study, an infusion of *M. vulgare* exhibited a decline in blood glucose levels by 50% and more than 60% concentrations of 100 mg/kg, 200 and 300 mg/kg respectively, as well as a significant lowering of total lipids, triglycerides and total cholesterol levels in treated animals [51]. Ghlissi et al. mentioned that hypoglycemic effect and the improvement of hepatorenal damage by *M. vulgare* infusion on alloxan-diabetic rats may in part be due to its antioxidant activity [54]. Some references have mentioned that *M. vulgare* is also used for the treatment of type 2 diabetes, hypercholesterolaemia and hypertension [54, 55].

Anti-bacterial activity

It was shown that the ethanol extract and the essential oil of *M. vulgare* had inhibitory effect against most *Staphylococcus aureus* isolates plates. The least MIC value of the extract *M. vulgare* was 2.5 mg/mL and the highest MIC value of the essential oil *M. vulgare* was 2.5 mg/mL [47]. Whereas, the essential oil of *M. vulgare* was effective on antibiotic resistance *Klebsiella pneumoniae* strains [58]. Another study showed that the essential oil of *M. vulgare* inhibited the growth of Gram (+) and Gram (-) bacteria (*Listeria monocytogene*, *Pseudomonas aeruginosa*, *Agrobacterium tumefaciens* and *Salmonella enterica*), along with IC50 and MIC values ranging from 0.1-15 µl/ml, respectively [57]. It was reported that the total phenolic and flavonoid contents of this plant have an antibacterial efficacy on *Candida albi*cans (yeast) [58]. In Morocco, the leaves and flowering tops of *M. vulgare* are used for diabetes treatment [55].

Anti-oxidant activity

Medicinal plants are a source of a wide variety of natural antioxidants. A significant radical scavenging effect of *M. vulgar*e was

reported by Fadel et al. [49]. In a study about the antioxidant potential of some Morocco medicinal plants the finding showed that phenolics in *M. vulgare* provided a substantial antioxidant activity [55].

Gastroprotective activity

It was reported that the extract of *M. vulgare* and marrubiin displays antiulcer activity and this effect can be partly attributed to the isolated diterpene [59].

Respiratory tract infection

Horehound has been used as an expectorant cough remedy since ancient Egyptian times [60]. Several usage of *M. vulgare* such as respiratory catarrh, acute and chronic bronchitis, whooping cough has been reported by Spiteri M. [54]. The leaves and flowering tops of *M. vulgare* are also used for bronchitis treatment in Morocco [55].

Traditional medicine (Ethnobotany)

Years ago, humans have relied on nature for their basic needs for the production of food stuff, shelters, clothing, means of transportation, fertilizers, flavors, and fragrances, and not the least, medicines. Indigenous people have been using the unique approach of their traditional system of medicine for centuries [61]. Medicinal plants are the "backbone" of traditional medicine, which means more than 3.3 billion people in the less developed countries utilize medicinal plants on a regular basis. There are nearly 2000 ethnic groups in the world, and almost every group has its own traditional medical knowledge and experiences [29]. *M. vulgare* as the most representative species has several traditional uses such as expectorant, antispasmodic properties, antiasthmatic, anti-infective agent and externally, it has been used to treat ulcers and wounds [31]. The plant is reported to possess hypoglycemic, antihypertensive, analgesic, anti-inflammatory, antioxidant, and antibacterial activities [30]. S. Dall'Acqua et al. has mentioned some of the traditional usage of the leaves of the plant such as Maltese fever, malarial fever, asthma, diaphoretic, dental abscesses, expectorant, emmenagogue, cirrhosis, hepatopathy, sedative, stomachic and dysmenorrhea, antipyretic and stomach disorders [62]. In a recent study about the antioxidant capacity and phenolic contents of some of the Mediterranean medicinal plants some of the traditional uses of *M. vulgare* such as treatment of gastroenterical and respiratory diseases, antinociceptive, anti-inflammatory, hypoglycemic and insecticidal effects were mentioned. Tonic, aromatic, expectorant, diaphoretic and diuretic activities have also been stated [63]. *M. vulgare* is used in folk medicine in Europe, Pakistan, Brazil, and Tunisia to treat respiratory infections, including bronchitis, coughs and asthma [30].

M. vulgare in Iranian Traditional Medicine

The crude extract of *M. vulgare* is widely used as antihypertensive in traditional medicine [50]. *M. vulgare* (Horehound, hoarhound) is one of the medicinal plants which is used in the treatment of stomach tonic, arrhythmia, asthma, jaundice, pulmonary diseases and liver disorders in Iranian traditional medicine [10, 64, 65]. In Alamut region of Ghazvin province in Iran the

plant are used traditionally for asthma, catarrh, cough, typhoid fever by the indigenous people [66].

Other effects and Medicinal uses

The medicinal properties of *M. vulgare* have been reported by many studies as follow: inflammatory and anti-oedematogenic effect [67], pulmonary affections and expectorant [68], source of natural antioxidants and increase of the anti-atherogenic potential of HDL (high-density lipoprotein) [69], cytotoxic activity [70], hepatoprotective activity [71], reducing the elevated blood glucose level and lipid profile of streptozotocin (STZ)-induced-diabetic rats [72], anti-tyrosinase effects [73], hepatoprotective properties [71], antispasmodic [74], poor digestion, loss of appetite, bloating and flatulence, treatment of diarrhoea, jaundice and painful menstruation. Additionally, externally is used for treatment of ulcers, skin damage, mouth and throat infections [54].

Conclusion

Since metabolic diseases count as the main dilemma in societies, so paying attention to the traditional medicine and medicinal plants for their treatment seems necessary. This study gives support to the traditional use of *M. vulgare* as a multipurpose herbal medicine and may justify its use in folk medicine.

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