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REVIEW ARTICLE: PHYTOCHEMISTRY AND PHARMACOLOGICAL ACTIVITIES OF MICROMERIA SPECIES

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ABSTRACT

Micromeria (Family Lamiaceae) is widespread across Europe, Asia, Africa, and North America, with a center of diversity in the Mediterranean region and the Canary Islands. More than 78 species of Micromeria are known. Several pharmacological activities have been reported, including antimicrobial, antioxidant, anticancer, and antidepressant effects. This review thoroughly discusses the chemical nature and classes of all isolated metabolites from Micromeria plants. A large group of chemical compounds, including mono-, di-, and triterpenoids, iridoids, flavonoids, steroids, phenolic compounds, saponins, coumarins, alkaloids, and tannins, have been reported from members of Micromeria species. Numerous studies focus on the isolation, chemical composition, and biological activities of the essential oils recovered from this species. The presence of volatile oils makes them valuable in the food, cosmetic, and pharmaceutical industries.

KEYWORDS: Micromeria, chemistry, terpenoids, flavonoids, Pharmacology.

INTRODUCTION

The Lamiaceae plant family is one of the largest families among the dicotyledons, including about 220 genera and nearly 4,000 species spread worldwide, most frequently in the Mediterranean region (Cantino et al., 1922; Harley et al., 2004; Heywood et al., 1972). In the

Republic of Moldova, the family is represented by 28 genera and 82 species. This large family is known for its vast number of species with medicinal, aromatic, culinary, and ornamental properties (Negru, 2007).

Lamiaceae species are very popular in folk medicine for treating various health problems such as throat infections, stomach disorders, ulcers, spasms, colds, hemorrhages, and skin problems. Species of this botanical family contain a wide variety of bioactive substances that make them very important from a pharmacological point of view. The family is also famous for the presence of essential oils, whose constituents have been found to be anti-inflammatory, hemostatic, cicatrizing, stomachic, sedative, spasmolytic, diuretic, expectorant, cardiac, and hypotensive, among other properties (Baser, 1993).

The medicinal properties of Lamiaceae species and their traditional use worldwide have attracted the attention of many scientists. This has led to intensive phytochemical investigations in the last few decades to prove the bases of their ethnobotanical uses and to identify new compounds in the hope of finding modern efficient drugs for various diseases (Negru, 2007). Recent studies have shown that medicinal plants belonging to the Lamiaceae family, particularly the subfamily Lamioideae, are very important for their antimicrobial, antifungal, antibacterial, and antioxidant activities (Ahmed et al., 2009; Armatu et al., 2010; Lugasi et al., 2006; Matkowsi et al., 2006). This family contains many species with potential therapeutic activity due to their content of essential oils (Baser, 1993).

Phytochemistry of Genus Micromeria

Micromeria (Family Lamiaceae) is found throughout North America, Europe, Africa, and Asia, with many varieties located in the Mediterranean region and Canary Islands (Bahramikia & Yazdanparast, 2012). Micromeria is also sometimes classified as part of the genus Satureja. The name Micromeria derives from the Greek roots mīkros (small) and meris (portion), reflecting the small size of their leaves and flowers (Quattrocchi, 2000). This perennial or dwarf shrub thrives in warm, rocky, and dry open habitats (Silic, 1979).

Volatiles (Terpenes)

The major volatiles of Micromeria species are presented in Table 1, and characteristic terpenoids of Micromeria species are shown in Figure 1. Micromeria species are especially rich in oxygenated monoterpenes. Among these, thymol and carvacrol are the most notable. Numerous studies indicate that these compounds are the main volatiles for M. cuneifolia, M.

hortensis, M. montana, M. spicigera, M. thymbra, and M. bachtiarica. Additionally, carvacrol is a key compound for M. khuzestanica. Thymol and carvacrol are followed by p-cymene and γ-terpinene. According to several reports, these compounds are the main volatiles of M. cuneifolia, M. hortensis, M. montana, M. sahendica, and M. thymbra (Bektas Tepe & Mustafa Cilkiz, 2016).

Micromeria species exhibit unusual chemical profiles. For example, piperitone, piperitenone, and piperitenone oxide are the main compounds of M. parvifolia and M. fruticosa (Beguinot, Cabana et al., 2013; Coelho et al., 2007, 2012; Dambolena et al., 2009; Lima et al., 2011; Luna et al., 2008; Viturro et al., 2000). Additionally, camphor has been identified as the major compound of M. visianii (Bezic et al., 2009; Dunkic & Bezic, 2008; Vidic et al., 2009).

Table 1: Major Terpenoids of Micromeria species.

NO	Major Terpenoids	Plant Species	Reference
1	*(-)*-Cadin-4-en-1-ol	*M. gilliesii*	Labbe et al. (1993)
2	*(+)*-T-cadinol		
3	*(+)*-Spathulenol	*M. sahendica*	Taherpour et al. (2008)
4	*(E)*-Nerolidol	*M. punctata*	Tariku et al. (2010)
5	*(Z)*-b-Ocimene	*M. montana*	Slavkovska et al. (2001)
6	1,8-Cineole	*M. atropatana*	Rustaiyan et al. (2004)
7	Eucalyptol	*M. boliviana*	Hatami et al. (2011)
8	Caryophyllene		
9	Bicyclogermacrene	*M. boliviana*	Viturro et al. (2000)
10	Borneol	*M. bachtiarica*	Hadian et al. (2012),
11	Caryophyllene oxide		
12	Bornyl acetate	*M. biflora*	Vagionas et al. (2007)
13	Camphene	*M. hortensis*	Kizil (2009)
14	Camphor	*M. douglasii*	Peer and Langenheim (1998)
15	Carvacrol	*M. atropatana*	Moradi et al. (2008)
16	Carvone	*M. atropatana*	Rustaiyan et al. (2004)
17	*cis*-3-Hexane-1-ol	*M. montana*	Mastelic and Jerkovic (2003)
18	*cis*-Jasmone	*M. bachtiarica*	Ahanjan et al. (2011b)
19	*cis*-Linalool oxide	*M. biflora*	Matasyoh et al. (2007)
20	*endo*-1-Bourbonanol		
21	Germacrene D		
22	*tau*-Cadinol		
23	a-Cadinol		
24	*cis*-Ocimene	*M. cuneifolia*	Biavati et al. (2004)
25	*cis*-Piperitenone epoxide	*M. parvifolia*	Lima et al. (2011)
26	*cis*-Piperitone oxide	*M. masukensis*	Vagionas et al. (2007)
27	*cis*-Terpinene	*M. hortensis*	Mumivand et al. (2011)
28	Citronellol	*M. glabrata*	Malagon et al. (2003)
29	Citronellyl acetate		

30	Isocaryophyllene		
31	Cymol	*M. hortensis*	Kizil et al. (2009)
32	Dihydrothymoquinone	*M. hortensis*	Taborsky et al. (2012)
33	Elemol	*M. isophylla*	Habibi et al. (2007)
34	a-Eudesmol		
35	Eugenol	*M. khuzestanica*	Farsam et al. (2004)
36	Farnesol	*M. Montana*	Djenane et al. (2012)
37	Geranial	*M. forbesii*	Ortet et al. (2009)
38	Geraniol	*M. hortensis*	Soran et al. (2011)
39	Geranyl acetate	*M. bachtiarica*	Ahanjan et al. (2011b)
40	Geranyl acetone	*M. bachtiarica*	Meshkatalsadat (2011)
41	Isomenthone	*M. abyssinica*	Tolossa et al. (2007)
42	Isopulegone	*M. brownei*	Rojas and Usubillaga (2000)
43	Limonene	*M. cuneifolia*	Mirjana et al. (2004)
44	Linalool	*M. bachtiarica*	Hadian et al. (2012)
45	Menthol	*M. atropatana*	Rustaiyan et al. (2004)
46	Menthone		
47	Methyl chavicol		
48	Methyl carvacrol	*M. montana*	Mirjana and Nada (2004)
49	Methyl thymol	*M. mittica*	Gohari et al. (2005)
50	*mid*-Spathulenol	*M. atropatana*	Gohari et al. (2005)
51	Myrcene (syn. b-Myrcene)	*M. cuneifolia*	Altun and Goren (2007)
52	Neral	*M. forbesii*	Ortet et al. (2009)
53	*o*-Ocimene	*M. cuneifolia*	Orhan et al. (2011)
54	*p*-Bisabolene	*M. montana*	Grosso et al. (2009a)
55	*p*-Cymen-8-ol	*M. montana*	Slavkovska et al. (2001)
56	*p*-Cymene	*M. aintabensis*	Azaz et al. (2005)
57	Piperitenone oxide	*M. fruticosa*	Coelho et al. (2007, 2012)
58	Piperitone		
59	Piperitone oxide		
60	Pulegone	*M. abyssinica*	Tolossa et al. (2007)
61	*rho*-Cymene	*M. intermedia*	Sadeghi et al. (2013)
62	Sabinene	*M. pseudosimensis*	Tchoumbougnang et al. (2009)
63	Spathulenol	*M. biflora*	Vagionas et al. (2007)
64	Terpinen-4-ol		
65	a-Bisabolol oxide-B		
66	Terpineol	*M. macrosiphonia*	Amiri (2011)
67	Tetradecane	*M. khuzestanica*	Kheirandish et al. (2011)
68	Thymohydroquinone	*M. hortensis*	Taborsky et al. (2012)
69	Thymol	*M. aintabensis*	Sampson et al. (2005)
70	Thymol methyl ether	*M. montana*	Radonic and Milos (2003b)
71	Thymoquinone	*M. atropatana*	Moradi et al. (2008)
72	(p-cymene-2,5-dione)	*M. cuneifolia*	Altun and Goren (2007)
73	*trans*-Sabinene hydrate	*M. horvatii*	Dardioti et al. (2010)
74	Viridiflorol	*M. visianii*	Vidic et al. (2009)
75	a-Bisabolol	*M. punctata*	Tariku et al. (2010)
76	a-Copaene	*M. subspicata*	Bezic et al. (2009)
77	a-Pinene	*M. cuneifolia*	Mirjana et al. (2004),

78	a-Terpinene	*M. cuneifolia*	Altun and Goren (2007)
79	a-Terpineol	*M. edmondi*	Sefidkon and Jamzad (2006)

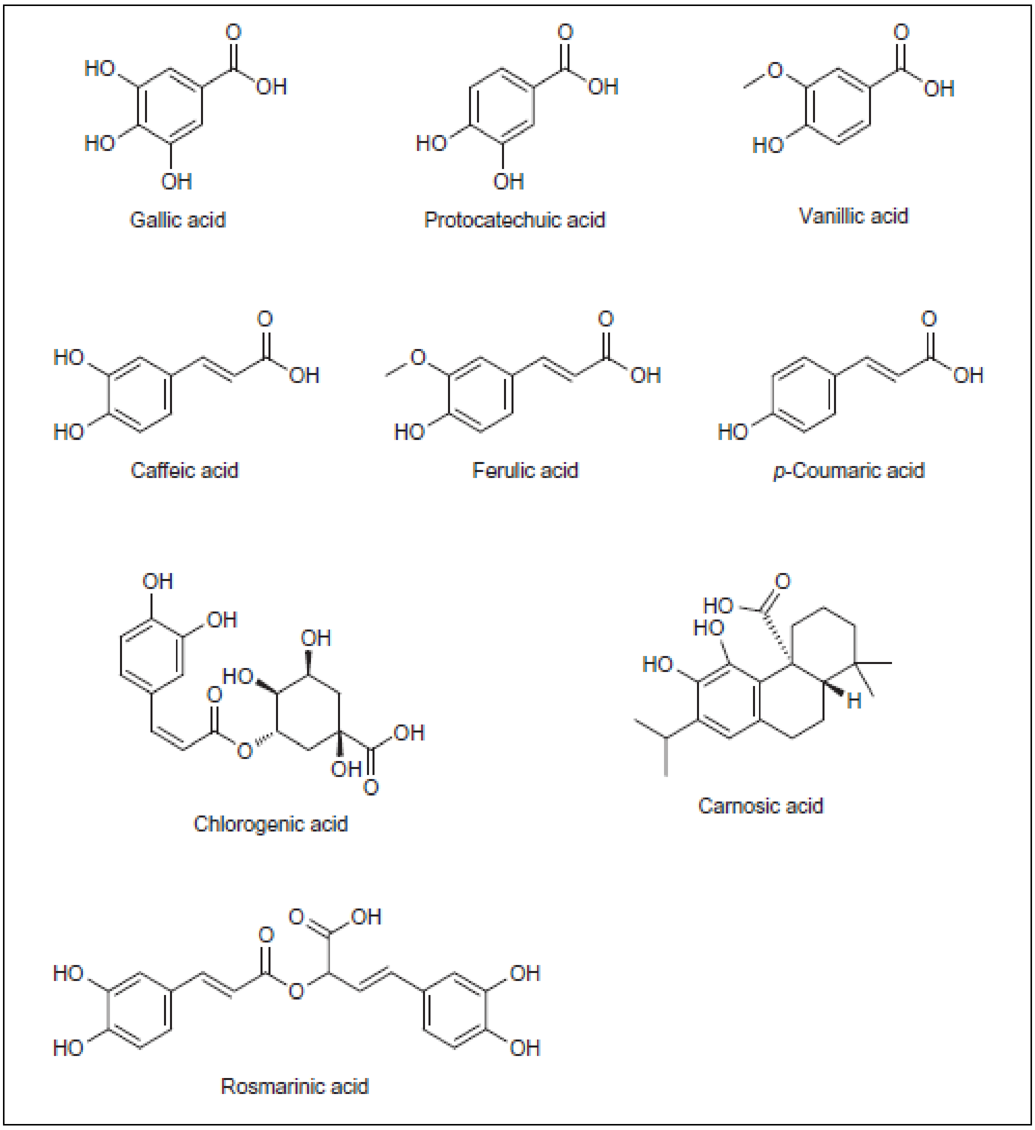

Figure (1): Common Terpenoids of Micromeria species.

Phenolic Acids

Phenolic acids identified in Micromeria species are listed in Table 2, and characteristic phenolic acids found in these species are shown in Figure 2.

The most common phenolic acid found in Micromeria species is rosmarinic acid. Caffeic acid is another significant phytochemical present in Micromeria species. It is notably found as one of the characteristic phenolic acids in M. cilicica, M. hortensis, M. icerica, and M. montana (Cetojevic-Simin et al., 2012; Giao et al., 2009; Kosar et al., 2005; Lung et al., 2013). Other phenolic acids detected in these species include p-coumaric, ferulic, gallic, chlorogenic, protocatechuic, vanillic, and carnosic acids (Bektas Tepe & Mustafa Cilkiz, 2016).

Table 2: Major phenolic acids of micromeria species.

NO	Major Phenolic acids	Plant Species	Reference
1	Rosmarinic acid	*M. aintabensis*	Askun et al. (2013)
2	*p*-Coumaric acid		
3	Ferulic acid		
4	Caffeic acid	*M. cilicica*	Cetojevic-Simin et al. (2012)
5	Gallic acid		
6	Chlorogenic acid	*M. montana*	Palavra et al. (2011),
7	Protocatechuic acid		
8	Vanillic acid		
9	Carnosic acid	*M. cuneifolia*	Kosar et al. (2003)

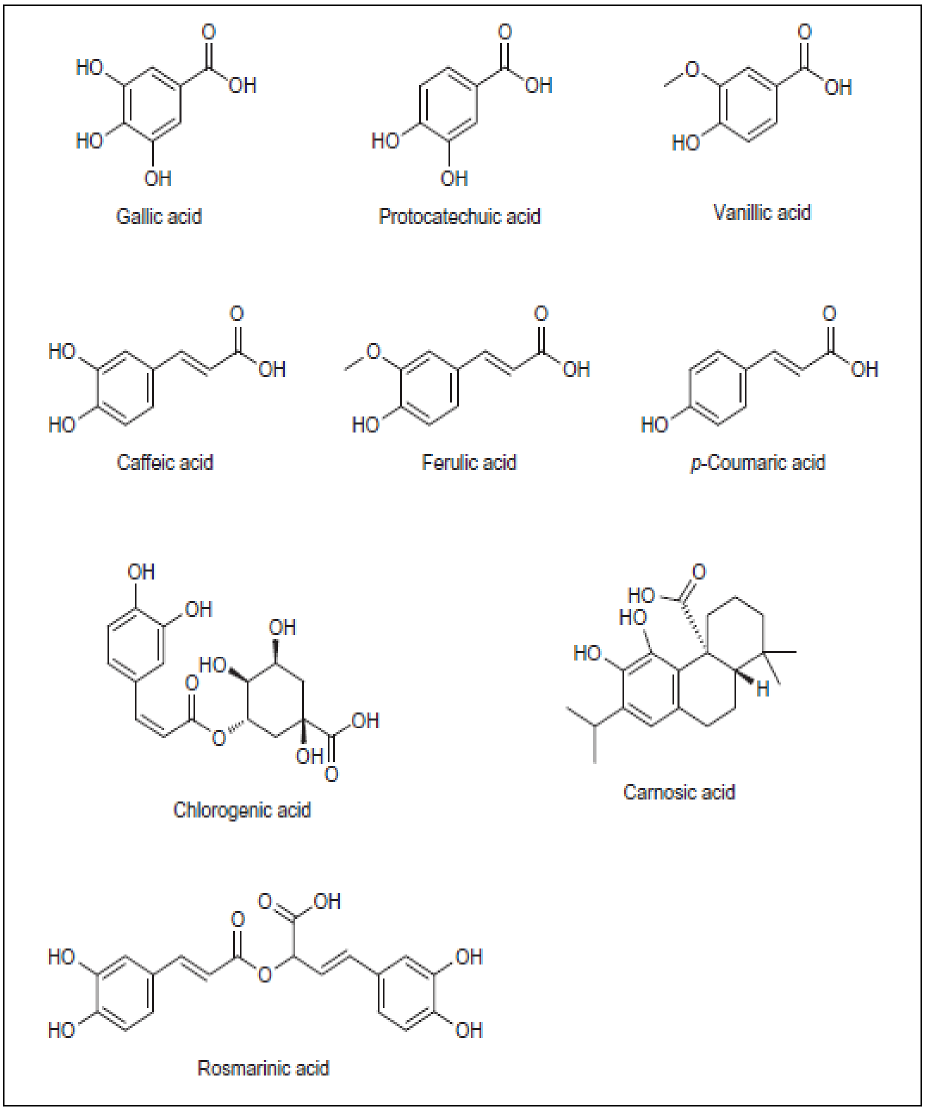

Figure (2): Common Phenolic acids of Micromeria species.

Flavonoids and Related Compounds

Flavonoids and related compounds found in Micromeria species are presented in Table 3, with the most common flavonoids illustrated in Figure 3.

According to the literature, five different flavonols—quercetin, epicatechin-3-O-gallate, epigallocatechin-3-O-gallate, kaempferol, and myricetin—have been identified in Micromeria species. Quercetin is the most commonly found flavonoid, occurring in M. aintabensis, M. cilicica, M. corulea, M. hortensis, M. icerica, M. montana, and M. sahendica (Alizadeh, 2011; Cetojevic-Simin et al., 2012; Exarchou et al., 2002; Kayedi et al., 2014). Flavan-3-ols, such as catechin and epicatechin (Cetojevic-Simin et al., 2012; Palavra et al., 2011; Silva et al., 2009), and flavanonols, such as aromadendrin and taxifolin (Malmir et al., 2012; Skoula et al., 2005), are other flavonoid aglycones found in these species.

Additionally, flavanone glucosides (naringin, naringenin glucoside, and hesperidin), flavone glucosides (vitexin, apigenin-7-glucoside, luteolin glucoside, and apigenin glucoside), and rutin (a flavonol glucoside) have been identified in M. cilicica, M. corulea, and M. icerica (Cetojevic-Simin et al., 2012).

Table 3: Major Flavonoids of Micromeria species.

NO	Major Flavonoids	Plant Species	Reference
A	***Flavones***		
1	Luteolin	*M. aintabensis*	Askun et al. (2013)
2	Apigenin		
3	Cirsilineol	*M. khuzestanica*	Malmir et al. (2012)
4	Cirsimaritin		
5	Genkwanin	*M. thymbra*	Skoula et al. (2005)
6	dimethyl ether		
7	Acacetin	*M. khuzestanica*	Malmir et al. (2012)
8	Diosmetin		
9	Diosmin	*M. macrostema*	Gutierrez (2013)
10	Ladanein	*M. thymbra*	Skoula et al. (2005)
11	Luteolin 7-methyl ether		
12	Thymusin	*M. spinosa*	Skoula et al. (2005)
B	***Flavonols***		
1	Quercetin	*M. aintabensis*	Askun et al. (2013)
2	Epicatechin-3-*O*-gallate	*M. parvifolia*	Cabana et al. (2013)
3	Epigallocatechin-3-*O*-gallate		
4	Kaempferol	*M. sahendica*	Sharifi et al. (2011)
5	Myrcetin		
C	***Flavanones***		

1	Naringenin	*M. aintabensis*	Askun et al. (2013)
D	***Flavan-3-ols***		
1	Catechin	*M. cilicica*	Cetojevic-Simin et al.(2012)
2	Epicatechin		
E	***Flavanonols***		
1	Aromadendrin	*M. khuzestanica*	Malmir et al. (2012)
2	Taxifolin		
F	***Flavanone glucosides***		
1	Hesperidin	*M. aintabensis*	Askun et al. (2013)
2	Naringin		
3	Naringenin glucoside	*M. hortensis*	Kosar et al. (2005)
4	Prunin	*M. macrostema*	Gutierrez (2013)
G	***Flavone glucosides***		
1	Vitexin	*M. cilicica*	Cetojevic-Simin et al.(2012)
2	Apigenin-7-glucoside		
3	Luteolin-glucoside	*M. hortensis*	Kosar et al. (2005)
4	Apigenin glucoside		
H	***Flavonol glucosides***		
1	Rutin	*M. cilicica*	Cetojevic-Simin et al.(2012)

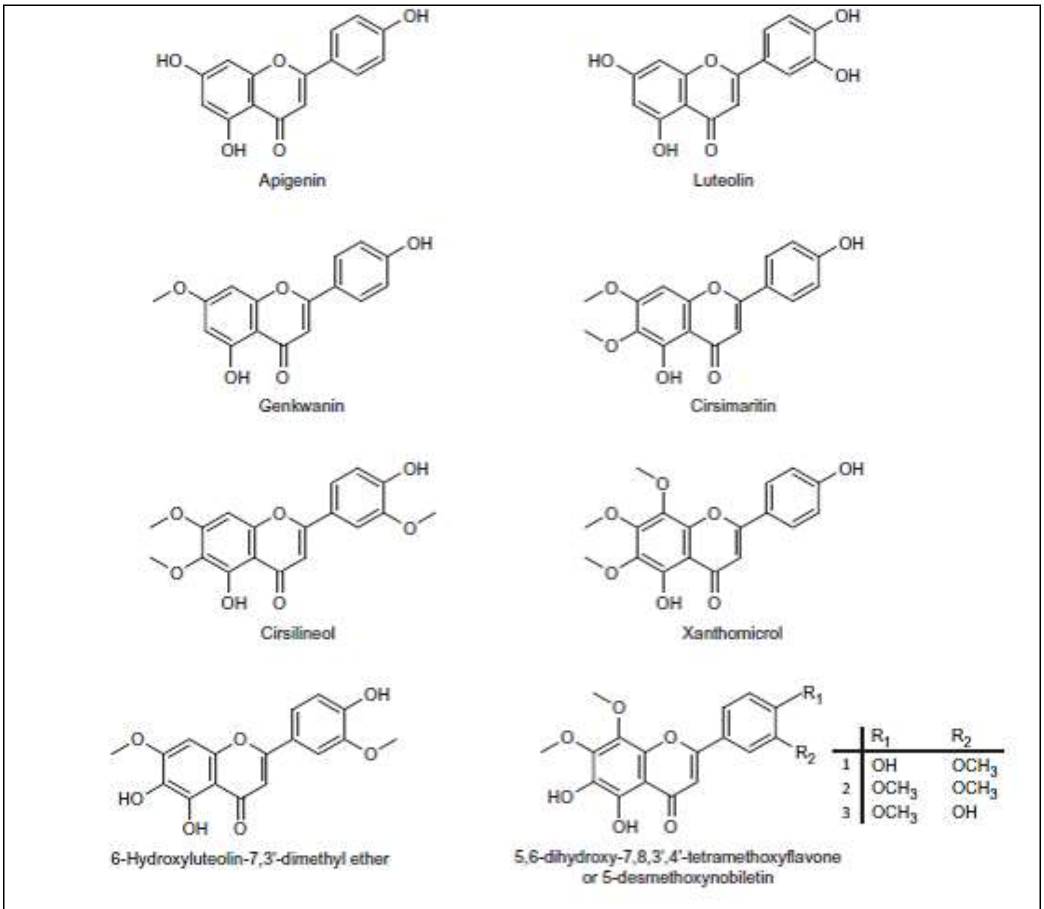

Figure (3): Common Flavonoids of Micromeria species.

Other Phytochemicals

The majority of studies have primarily focused on fatty acids. Kitic et al. (1999) reported the presence of linoleic, linolenic, palmitic, and oleic acids in Micromeria adamovicii and Micromeria fukarekii. Additionally, Goren et al. (2003) identified fatty acids in Satureja cuneifolia and Satureja thymbra, including 9-octadecenoic acid methyl ester, hexadecanoic acid methyl ester (methyl palmitate), 9,12,15-octadecatrienoic acid methyl ester, and octadecanoic acid methyl ester.

According to the literature, Micromeria hortensis is the only species evaluated for its enzyme content. Enzymes identified in this species include flavocytochrome b, cytochrome b, NAD-independent lactate dehydrogenase, peroxidase isoenzymes, o-dianiside peroxidases, lignin peroxidase, ascorbate peroxidase, and superoxide dismutase. Data regarding tocopherols (α-, β-, γ-, δ-tocopherols), triterpene acids (ursolic, oleanolic, and betulinic acids), phytosterols (β-sitosterol and β-sitosterol-3-O-β-D-glucopyranoside), alkane homologues (nonacosane and hentriacontane), nubigenol (a dihydrochalcone), and erigeroside are also available (Arzi et al., 2008, 2010; Keyhani, 2006; Keyhani et al., 2009; Paknia et al., 2006).

Inorganic Compounds

In addition to the organic phytochemicals mentioned, inorganic compounds in Micromeria species have also been reported. Dunkic and Bezic (2009) analyzed the mineral composition of Micromeria croatica and found significant amounts of calcium, potassium, and magnesium. Additionally, trace elements such as iron, copper, zinc, and manganese were also detected in this species.

Pharmacological Activities

Antimicrobial Activity

The antimicrobial activity of Micromeria species has been extensively studied, with many species showing significant antibacterial and antifungal effects. For instance, Micromeria thymbra essential oil exhibited strong antibacterial activity against Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa (Cosentino et al., 1999). Similarly, Micromeria fruticosa essential oil showed potent antifungal activity against Candida albicans and Aspergillus niger (Bowers et al., 1976).

Antioxidant Activity

Micromeria species are rich in phenolic compounds, which are known for their antioxidant properties. The antioxidant activity of Micromeria species has been demonstrated in various studies. For example, Micromeria croatica exhibited strong antioxidant activity in DPPH radical scavenging assays (Skoula et al., 2005). The high content of rosmarinic acid in Micromeria species contributes significantly to their antioxidant potential.

Anti-inflammatory Activity

The anti-inflammatory properties of Micromeria species have been investigated in several studies. Essential oils from Micromeria species, such as Micromeria graeca, have shown significant anti-inflammatory effects in animal models (Flemmig et al., 2012). The presence of thymol and carvacrol in these essential oils is believed to contribute to their anti-inflammatory activity.

Anticancer Activity

Recent studies have explored the anticancer potential of Micromeria species. For instance, Micromeria fruticosa extract exhibited cytotoxic effects against human breast cancer cell lines (MCF-7) (Cetojevic-Simin et al., 2012). The presence of flavonoids and phenolic acids in Micromeria species is thought to play a role in their anticancer activity.

Antidepressant Activity

The antidepressant activity of Micromeria species has also been reported. For example, Micromeria fruticosa essential oil demonstrated significant antidepressant effects in animal models of depression (Amin et al., 1996). The bioactive compounds in Micromeria species, such as thymol and carvacrol, are believed to contribute to their antidepressant properties.

CONCLUSION

Micromeria species are rich sources of bioactive compounds, including terpenoids, flavonoids, phenolic acids, and essential oils. These compounds contribute to the significant pharmacological activities of Micromeria species, such as antimicrobial, antioxidant, anti-inflammatory, anticancer, and antidepressant effects. The diverse chemical composition and wide range of biological activities make Micromeria species valuable in the fields of medicine, pharmacy, and cosmetics. Further research is needed to explore the full potential of Micromeria species and to develop novel therapeutic agents from these plants.

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