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Review Article

The genus *Micromeria* Benth.: An overview on ethnobotany, chemotaxonomy and phytochemistry

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ABSTRACT

The genus *Micromeria* Benth. from the family Lamiaceae mainly comprises herbaceous plants having several remarkable ethnobotanical, biological and phytochemical applications. This review critically appraises all the information available in the literature, *e.g.*, Scopus, Institute for Scientific Information-Web of Science (ISI-WOS) as well as Medline on various species of this genus covering aspects of biological activity, ethnobotanical, chemical taxonomy and phytochemistry. The phytochemical composition of both essential oils and non-volatile extracts is reported. Their chemotaxonomic implications and ethnomedicinal impacts are also discussed. The pharmacological properties of crude extracts and isolated phytochemicals from *Mircomeria* spp. observed in several bioactivity tests are also critically reviewed. From phytochemical point of view, the characterization of the organic extracts of different *Mircomeria* spp. has led to the identification of some valuable natural compounds. Furthermore, the chemical profiles of most of the species are dominated by oxygenated monoterpenes. A wide spectrum of promising biological properties have been attributed to *Mircomeria* species including antibacterial, antifungal, antioxidant, anticholinesterase, tyrosinase inhibition and antinociceptive activities. Moreover, it has been shown that rosmarinic acid serves as a marker compound in several entities of this genus.

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1. Introduction

From the time immemorial, medicinal plants have been extensively used in the traditional medicine systems of many countries for the maintenance of health and well being (Wansi et al., 2018, 2019; Hussain and Mazumder, 2021; Silva et al., 2021; Yousefi et al., 2021). In the modern medical science and a wide spectrum of the relevant disciplines comprising pharmaceutical, pharmacological fields among others, these plants are of vital importance to treat a broad range of persistent diseases (Mohammadhosseini, 2016). According to the statistics given by the Food and Agriculture Organization in 2002, around 50,000 medicinal plants exist in different parts of the world (https://en.wikipedia.org/wiki/Medicinal_plants; Schippmann et al., 2002; Sher et al., 2014). Of course, it seems rational that these plants could be considered as proper alternatives for a wide range of chemical drugs with a number of unpleasant and dangerous side effects to the human body (Ganesan and Xu, 2017). In fact, medicinal plants are rich sources of valuable natural compounds, like terpenoids (Mohammadhosseini et al., 2021), coumarins (Mohammadhosseini et al., 2017; Bailly, 2021; Nahar and Sarker, 2021), flavonoids (Mohammadhosseini, 2017; Allam, 2020; Moncayo et al., 2021; Thagriki, 2022), phenolic compounds (Vladimir-Knežević et al., 2011; Brahmi et al., 2017; Mohammadhosseini et al., 2019), iridoids (Venditti et al., 2018; Frezza et al., 2019a; Nahar and Sarker, 2021), proazulenes (Glasl et al., 1999; Radušiene and Gudaityte, 2005; Mohammadhosseini et al., 2017), sesquiterpenoids (Mohammadhosseini et al., 2017; Opiyo, 2019; Asadi et al., 2022), etc. The Lamiaceae is a large family of aromatic plants, comprising *ca*. 220 genera and 4000 species. Most of the species of this family are frequently used as condiments, and for culinary and medicinal purposes

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worldwide (Hammer et al., 2005; Bianchi, 2015). The majority of the Lamiaceae plants possess pleasant odor and have pharmaceutical and medical applications. The fragrance is mainly related to the presence of external glandular structures in most of these plants and this morphologic feature is particularly developed in plants belonging to the Lamiaceae family (Giuliani and Maleci Bini, 2008; Venditti et al., 2013b; Venditti et al., 2014b; Venditti et al., 2015c; Venditti et al., 2016a). Similar to many other species of this family, most of the fragrant *Micromeria* species are endemic in the Mediterranean region. In Table 1, some of the most important endemic species from this genus have been listed in different countries whose data are available in the literature. In fact, the genus *Micromeria* belonging to tribe Mentheae and subfamily Nepetoideae (Lamiaceae) with approximately 130 species contains a variety of aromatic plants most of which produce essential oils (EOs) (Slavkovska et al., 2005). This genus has a wide distribution area from South Africa to west of Europe to Asia with a large number of perennial plants, involving 70-90 dwarf shrubs as well as subshrubs (Wielgorskaya and Takhtadzhian, 1995). Taking into account the morphological features along with phylogenetic relationships, different species of the genus *Micromeria* can be classified into four categories comprising *Cymularia* Boiss., *Micromeria*, *Pseudomelissa* Bentham and *Pineolentia* P. Perez (Harley et al., 2004; Stojičić et al., 2016). The *Micromeria* species often grow wild in the mountainous, open habitats or rocky areas of the world, as well. In Europe, about twenty-two species of *Micromeria* exist; their distribution is mostly concentrated in the Balkan Peninsula (Kremer et al., 2014a). In Canary Islands, this genus comprises about 16 species among which most species are endemic in this region (Puppo et al., 2014). In the flora of Iran, Turkey as well as Serbia and Montenegro, the genus *Micromeria* comprises 3, 14 and 10 species of which 2, 12 and 7 species are, respectively, endemic (Tabanca et al., 2001; Slavkovska et al., 2005). The endemic Iranian *Micromeria* species are *M. hedgei* Rech. F. and *M. persica* Boiss. (Sefidkon and Kalvandi, 2005). The main goal of this review paper is to integrate the data available within the recent decades on phytochemistry, chemotaxonomy, ethnobotany and biological activities of different *Micromeria* species. To collect the relevant data, the Scopus database (date access: 7 July 2022) and revisited on 26 July 2022, original research articles published by Elsevier, Springer, Taylor and Francis along with some of the other reliable and relevant English and non-English scientific sources were systematically investigated.

2. Results and Discussion

2.1. Chemical profiles of the extracted essential oils (1989 to date)

Essential oils (EOs) are mixtures of a variety of volatile natural compounds and are extracted by distillation as hydrophobic liquids. These liquids are often lighter than water and could be easily separated at the end of the extraction process. The common techniques which have been traditionally used for the isolation of EOs mainly involve expression, cold press, water-distilled extraction and steam distillation (Shafaghat et al., 2017). However, during the recent decades, some advanced approaches have been described in the literature for the extraction of these secondary metabolites. Most recent methods utilized for this purpose involve microwaves, namely microwave assisted hydrodistillation (MAHD) (Hashemi-Moghaddam et al., 2018) and solvent free microwave extraction (SFME) (Nekoei and Mohammadhosseini, 2017). On the other hand, to study the spontaneous emission of volatiles from different organs of the plant materials, a technique based on completely different principles has been successfully used. This technique, namely headspace-solid phase microextraction (SPME) consists of the adsorption/absorption of volatile analytes on a large number of organic fibers (Mohammadhosseini et al., 2016; Nekoei and Mohammadhosseini, 2017). Quantitative and qualitative screening of the chemical profiles of different EOs from the genus *Micromeria* has been the subject of several reports in the literature. The majority of these reports deal with the sampling areas located in the Middle East, east of Europe along with some African countries. A simple perusal of the data tabulated in Table 2 demonstrates that in most of the reported profiles of the *Micromeria* EOs, oxygenated monoterpenes (OM) particularly pulegone (Fleisher and Fleisher, 1991; Kirimer, 1992; Tucker et al., 1992; Kirimer et al., 1993a; Kirimer et al., 1993b; Baser et al., 1996; Duru et al., 2004; Šavikin et al., 2010; Arslan, 2012; Radulović and Blagojević, 2012; Shehab and Abu-Gharbieh, 2012; Alwan et al., 2016; Salameh et al., 2018), piperitenone oxide (Kirimer et al., 1991; Stojanovic et al., 1999; Marinković et al., 2002), geranial (Ding et al., 1994; Mallavarapu et al., 1997; Alizadeh and Ranjbaran, 2017; Tošić et al., 2019), borneol (Kremer et al., 2012), linalool (Tzakou and Couladis, 2001; Telci and Ceylan, 2007; Masoudi et al., 2009), isomenthone (Slavkovska et al., 2005), isoborneol (Stojanović et al., 2006), verbenol (Stojanović et al., 2006), piperitone epoxide (Bukvički et al., 2016), pinocarvone (Ruscic et al., 2017), thymol (Sefidkon and Kalvandi, 2005; El-Seedi et al., 2008) and menthone (Zheljazkov et al., 2019) have been identified as the main components. Non-terpene hydrocarbons (NH) were also characterized as the major groups of components of some other oils of *Micromeria* species, with isoeugenol (El-Hawary et al., 1991), (*Z*)-3-hexenol (El-Seedi et al., 2008) and fatty acids like *n*-hexadecanoic acid (Jafari et al., 2018). In addition, in the chemical profiles of the volatile EOs dominated by high frequency of oxygenated sesquiterpenes (OS), the main constituting compounds were reported as spathulenol (Slavkovska et al., 2005; Palić et al., 2010; Kremer et al., 2014b), α-bisabolol (Vuko et al., 2012) and caryophyllene oxide (Tzakou and Couladis, 2001; Kremer et al., 2014a; Vuko et al., 2019). On the other hand, in the EOs of *Micromeria* species with high quantities of

Table 1
The available list concerning some endemic species from the genus *Micromeria*.

Country flora	Endemic species		Ref.
	Number	Name	
Algeria and Morocco	1	*M. debilis* Pomela	(Gherib et al., 2016)
Balkan peninsula	3	*M. croatica* (Pers.) Schott, *M. tbytnifolia* and *M. albanica* (Griseb. ex K. Maly) Silic	(Stojanovic et al., 1999)
Bulgaria	4	*M. juliana* (L.) Bentham ex Reichenb., *M. cristata* (Hampe) Griseb, *M. dalmatica* Bentham ssp. *bulgarica* (Velen.) and *M. frivaldszkyana* (Degen) Velen.	(Jordanov, 1989)
Croatia	2	*M. croatica* (Pers.) Schott and *M. thymifolia* (Scop.) Fritsch	(Vladimir-Kneževic et al., 2011)
Iran	2	*M. hedgei* Rech. F. and *M. persica* Boiss.	(Sefidkon and Kalvandi, 2005)
Italy	1	*M. fruticulosa* (Bertol.) Grande (syn. *Satureja fasciculata* Rafn; *Satureja approximata* Biv.)	(Formisano et al., 2007)
Lebanon	2	*M. barbata* Fisch. & C.A.Mey. and *M. libanotica* Boiss.	(Hilan et al., 2011)

[a] Also known as Satureja briquetii Maire

sesquiterpene hydrocarbons (SH), the most abundant natural compounds were β-caryophyllene (Özek et al., 1992; Al-Rehaily, 2006; Formisano et al., 2014; Vuko et al., 2019) and germacrene D (Baser and Demirçakmak, 1997). Slavkovska et al. (2005) described the chemical compositions of *M. thymifolia* (Scop.) Fritsch (five samples), *M. dalmatica* Benth., *M. pulegium* (Rochel) Benth., *M. albanica* (Griseb. ex K. Maly) Silic, *M. croatica* (Pers.) Schott, *M. juliana* (three samples), *M. cristata* and *M. parviflora* (three samples). All of these plants were collected from limestone sampling areas under the sub-Mediterranean climatic conditions. Four species and their respective samples, namely *M. thymifolia* (Scop.) Fritsch, *M. dalmatica* Benth., *M. pulegium* (Rochel) Benth. and *M. albanica* (Griseb. ex K. Maly) Silic were characterized by remarkable quantities of oxygenated monoterpenes (OM) (Table 2). Accordingly, natural compounds like pulegone, piperitenone, piperitenone oxide, isomenthone and piperitone oxide were distinguished as the major constituents of the oil. Furthermore, in *M. croatica* (Pers.) Schott, *M. juliana* and *M. cristata*, oxygenated sesquiterpenes like caryophyllene oxide and spathulenol constituted most of the profiles. However, only one EO sample was reported related to *M. parviflora* in which, despite the negligible difference in total amounts, oxygenated sesquiterpenes and oxygenated monoterpenes were among the prevailing natural compounds. In the report of Stojičić et al. (2016) on the EOs from the aerial parts (shoots) of *M. pulegium* (Rochel) Benth. from Serbia, pulegone and menthone had, respectively, the first and second ranks among the recognized compounds from the frequency point of view for all samples involving wild growing plants, micropropagated plants (M.P.) comprising plants grown on plant growth regulator-free medium (PG-PGRFM) as well as plants grown on medium supplemented with 10 μM N^6-benzyladenine (PGMSBA). The chemical compositions of the EOs of wild samples of *M. croatica* (Pers.) Schott along with two of its micropropagated oil samples have been reported recently (Tošić et al. (2019). Of the micropropagated samples, one was treated without plant growth regulators (PGR), while the other sample was subjected to an interval of four-week time. The results obtained by gas chromatographic-based techniques, involving GC-FID and GC-MS followed by complementary spectral assignments for the EOs isolated from the wild samples revealed the prevalence of oxygenated monoterpenes (OM) among which borneol was the major compound, followed by the sesquiterpene hydrocarbons like α-cadinene and bicyclic monoterpene hydrocarbons like β-vetivenene. Furthermore, for the oil sample without PGR, borneol and geranial were reported as the major characterized components. These results suggest that the plant growth regulators may have a role in the modulation of the biosynthetic pathways

Table 2
Main components of essential oils, volatile constituents and extracts from different species of the genus *Micromeria* in different parts of the world.

Plant name (s)	Main components (%)	VOY [a]	Number of identified compounds/ Total percentage	Dominant group/ Extraction method (s)/ Characterization methods (s)	Part(s)/Country	Ref.
M. albanica (Griceb. ex K. Mal) Silic´	piperitenone oxide (44.0%), pulegone (20.7%), piperitone oxide (8.9%) and piperitone (7.5%)	0.9	9/91.5	OM [b] / HD [c] / Preparative GC, GC and GC/MS	Aerial parts/ Serbia	(Stojanovic et al., 1999)
	piperitenone oxide (38.7%), pulegone (13.4%), piperitenone (9.7%), piperitone (5.6%) and limonene (3.2%)	0.88	17/82.3	OM / HD / GC and GC/MS	Leaves/ Yugoslavia	(Marinković et al., 2002)
	piperitone oxide (36.9%), piperitenone oxide (21.9%), piperitenone (10.0%), pulegone (7.8%), limonene (7.0%) and spathulenol (2.3%)	NR [d]	34/97.9	OM / HD / GC and GC/MS	Aerial parts/ Serbia and Motenegro	(Slavkovska et al., 2005)
M. barbata Fisch. & C.A.Mey.	pulegone (20.2%), limonene (16.6%), neomenthol (12.4%), menthol (6.2%), piperitone (4.2%) and β-pinene (3.3%)	2	17/70.6	OM / CSD [e]/ GC and GC/MS	Aerial parts/ Lebanon	(Alwan et al., 2016)
M. biflora (Buch. Ham. ex D. Don) Benth.	geranial (50.5%) and neral (37.1%)	0.3	11/89.0	OM / HD / GC/MS	Whole plant/ China	(Ding et al., 1994)
	Summer: geranial (36.7%) and neral (25.3%)	0.2	45/92.7	OM / HD / GC and GC/MS	Aerial parts/ India	(Mallavarapu et al., 1997)
	Winter: geranial (41.3%) and neral (32.0%)	0.32	52/95.9			
	trans-caryophyllene (43.7%), caryophyllene oxide (18.0%), spathulenol (8.5%), α-humulene (4.6%), α-myrcene (3.1%) and germacrene-D (3.1%) f	0.07	30/98.2	SH / HD / GC/MS	Aerial parts/ Saudi Arabia	(Al-Rehaily, 2006)
M. brownei (Swartz) Benth.	pulegone (51.7%), menthone (20.9%), neomenthol (11.9%) and germacrene D (3.39%) g	0.13	12/99.6	OM / HD / GC and GC/MS	Aerial parts /USA	(Tucker et al., 1992)
M. carminea P.H. Davis	borneo1 (26.0%), camphor (10.6%) and cedrol (5.4%)	0.14	55/74.9	OM / HD / GC and GC/MS	Aerial parts/ Turkey	(Baser et al., 1995)
M. cilicica Hausskn. ex P.H.Davis	pulegone (66.6%), *cis-p*-menthone (21.7%) and *trans-p*-menthone (9.6%)	0.88	34/98.9	OM / HD / GC, GC/MS, ^{1}H NMR and ^{13}C NMR	Aerial parts/ Turkey	(Duru et al., 2004)
	pulegone (64.1%), *cis-p*-menthone (25.3%), *trans-p*-menthone (5.6%) and nerol (2.5%)	0.55	30/99.3	OM / SD / GC, GC-MS, ^{1}H NMR and ^{13}C NMR		
M. congesta Boiss. et Hausskn. ex Boiss	piperitenone oxide (40.0%), pulegone (11.8%) and verbenone (8.3%)	NR	40/91.5	OM / SD /CC [h], GC and GC/MS	Above-ground parts/ Turkey	(Kirimer et al., 1991) (Herken et al., 2012)
	piperitenone oxide (45.0%), pulegone (9.7%) and verbenone (9.4%)		40/93.0	OM / HD / CC [h], GC and GC/MS		
	piperitone oxide (39.2%), pulegone (24.2%) and *trans*-piperitone epoxide (4.9%)	3.2	66/95.2	OM / SD / GC/MS	Aerial parts/ Turkey	
M. cremnophila Boiss. et Heldr.	germacrene D (24.0%), β-caryophyllene (23.0%), caryophyllene oxide (9.9%), bicyclogermacrene (6.8%) and (E)-β-farnesene (6.4%)	0.02	70/91.5	SH [i]/ HD / GC/MS	Aerial parts/ Turkey	(Baser and Demirçakmak, 1997)
M. cristata (Hampe) Griseb.	Sample A: From Afyon Region: borneol (26.9%), camphor (14.5%) and caryophyllene oxide (3.7%) j	0.05	108/89.6	OM / HD / GC/MS	Aerial parts/ Turkey	(Tabanca et al., 2001)
	Sample B: From Isparta Region: borneol (31.4%), camphor (9.1%) and caryophyllene oxide (5.5%) j	0.03	86/86.7			
	Sample C: From Kutahya Region: borneol (39.3%), camphor (10.7%) and caryophyllene oxide (3.8%) j	0.08	61/89.1			
	spathulenol (11.7%), camphor (7.5%), globulol (6.0%), borneol (5.7%), 1,8-cineole (5.0%), α-cadinol (4.3%), bornyl acetate (4.1%), (*E*)-nerolidol (3.9%) and *cis*-thujone (3.1%)	NR	51/87.7	OS [k]/ HD / GC and GC/MS	Aerial parts/ Serbia and Motenegro	(Slavkovska et al., 2005)

Table 2 Continued

Plant name (s)	Main components (%)		VOY [a]	Number of identified compounds/ Total percentage	Dominant group/ Extraction method (s)/ Characterization methods (s)	Part(s)/Country	Ref.
M. cristata (Hampe) Griseb.	isoborneol (11.3%), borneol (8.5%), verbenone (8.2%), 10-*epi*-α-cadinol (8.2%) and thujan-3-ol (8.0%)		0.1	37/95.9	OM / HD / GC and GC-MS	Aerial parts/ Serbia	(Stojanović et al., 2006)
M. croatica (Pers.) Schott	caryophyllene oxide (24.4%), δ-cadinene (10.9%), borneol (10.8%), piperitenone (10.0%) and α-muurolol (8.1%),		NR	50/94.9	OS / HD / GC and GC/ MS	Aerial parts/ Serbia and Motenegro	(Slavkovska et al., 2005)
	W.G.P. [l]: borneol (25.3%), α-cadinene (16.8%), and β-vetivenene (10.5%)		0.21	35/91.0	OM / HD / GC-FID and GC/MS	Aerial parts/ Serbia	(Tošić et al., 2019)
	MPM [m]:	**GWPGR** [n]: borneol (20.3%), geranial (11.9%) and *cis-p*-mentha-1(7),8-dien-2-ol (8.06%)	0.14	37/82.2			
		SWK [o]: geranial (33.5%) and *cis-p*-mentha-1(7),8-dien-ol (23.7%)	0.45	36/93.0			
	Bojinac locality: β-caryophyllene (25.2%), caryophyllene oxide (10.1%), limonene (3.9%), linalool (3.5%), α-cubebene (3.5%), γ-terpinene (3.5%) and viridiflorol (3.3%)		NR	39/94	SH / HD / GC and GC/ MS	Aerial parts/ Croatia	(Vuko et al., 2019)
	Bacickuk locality: caryophyllene oxide (21.1%), linalool (6.4%), limonene (5.9%), geraniol (5.1%), neryl acetate (4.9%), α-terpinene (4.2%), thymol methyl ether (3.3%) and camphor (3.1%)			38/92.4	OM / HD / GC and GC/MS		
	Stupacinovo locality: caryophyllene oxide (20.2%), β-caryophyllene (10.2%), camphor (6.8%), thymol acetate (5.4%), α-terpinene (5.1%), caryophyllene acetate (4.9%), myrtenol (3.6%) and β-bisabolol (3.0%)			42/90.8	OS / HD / GC and GC/ MS		
M. dalmatica Benth.	piperitenone oxide (41.8%), pulegone (15.9%), piperitenone (10.2%), limonene (5.8%) and piperitone (3.4%)		1.11	22/91	OM / HD / GC and GC/MS	Leaves/ Yugoslavia	(Marinković et al., 2002)
	piperitenone (56.7%), pulegone (12.1%), limonene (8.3%), piperitone (3.3%) and spathulenol (1.3%)		NR	37/94.9	OM / HD / GC and GC/MS	Aerial parts/ Serbia and Motenegro	(Slavkovska et al., 2005)
	pulegone (26.7%), piperitenone (21.8%) and piperitenone oxide (25.4%)		0.8	34/98.7	OM / HD / GC and GC/MS	Aerial parts/ Montenegro	(Šavikin et al., 2010)
	limonene (3.4-25.5%), menthone (0.0-33.3%), isomenthone (0.0-24.7%), pulegone (0.4-46.4%), piperitenone (0.0-10.5%) and germacrene D (0.2-14.6%) [p]		0.2 - 1.5	57/97.2-99.4 [p]	OM / HD / GC/MS	Aerial parts/ Greece	(Karousou et al., 2012)
	pulegone (29.6%), menthone (11.7%) and piperitenone (10.8%)		1.5	116/93.6	OM / HD / GC and GC/MS	Above-ground parts/	(Radulović and Blagojević, 2012)
	piperitenone (41.5%), pulegone (19.0%), piperitenone oxide (14.5%), D-limonene (6.2%) and *p*-menthone (5.1%)		1.36	13/98.8	OM / SPME-GC/MS	Aerial parts/ Serbia	(Bukvicki et al., 2015)
M. debilis Pomel	β-pinene (19.3%), germacrene D (11.4%), geranial (8.7%), caryophyllene oxide (8.0%), (E)-β-caryophyllene (8.0%) and linalool (6.5%)		0.07 - 0.12	42/92.4	MH / HD / GC(FID), GC/ MS and ^{13}C-NMR	Aerial parts/ Algeria	(Gherib et al., 2016)
M. dolichodontha P. H. Davis	germacrene D (24.0%) β-caryophyllene (23.0%), caryophyllene oxide (9.9%), bicyclogermacrene (6.8%) and (E)-β-farnesene (6.4%) [q]		0.02	70/91.5	OM / HD / GC/MS	Aerial parts/ Turkey	(Başer et al., 1997)

Table 2 Continued

Plant name (s)	Main components (%)	VOY [a]	Number of identified compounds/ Total percentage	Dominant group/ Extraction method (s)/ Characterization methods (s)	Part(s)/Country	Ref.
M. frivaldszkyana (Degen) Velen.	Uzana region: Dry sample: menthone (56.3%), pulegone (20.5%), neomenthol (7.8%) and limonene (2.6%)	0.18	44/98.1	OM / HD / GC-FID and GC/MS	Above ground plant parts/ Bulgaria	(Zheljazkov et al., 2019)
	Shipka region: Dry sample: pulegone (50.5%), menthone (18.4%), limonene (10.1%), germacrene D (3.4%) and neomenthol (2.4%) Fresh sample: pulegone (61.2%), menthone (16.6%), limonene (6.9%) and germacrene D (3.5%)	0.26	72/98 68/99.1			
M. fruticosa (L.) Druce	pulegone (62.0-65.2%), *iso*-menthol (6.9-7.3%), β-caryophyllene (2.7-4.3%), piperitenone oxide (2.9-4.6%), and piperitenone (1.8-2.0%) [r]	2.4	51/92.6	OM / SD / GC and GC/MS	Aerial parts /USA	(Fleisher and Fleisher, 1991)
	pulegone (57.2%) isomenthone (20.9%) and menthone (8.5%) [s]	2.6	42/98.4	OM / HD / GC and GC/MS	Aerial parts/ Turkey	(Kirimer, 1992)
	pulegone (33.4%) and piperitenone (33.1%) [t]	0.65	49/93.0			(Kirimer et al., 1993a)
	pulegone (81.3%) and piperitenone (3.1%) [u]	4.03	36/94.0			(Kirimer et al., 1993b)
	pulegone (39.6%), menthol (24.3%) and menthone (24.2%) [v]	2	36/>90			(Baser et al., 1996)
	piperitone (50.6%), pulegone (29.2%) and isomenthone (3.9%) [w]	1.85	29/93.4	OM / HD / GC/MS	Aerial parts/ Turkey	(Güllüce et al., 2004)
	M. fruticosa subsp. *serpyllifolia*: linalool (30.3%), pulegone (16.6%) and *p*-menthone (10.3%)	2.4	27/96.7	OM / HD / GC/FID and GC/MS	Aerial parts/ Turkey	(Telci and Ceylan, 2007)
	M. fruticosa subsp. *brachycalyx*: linalool (39.9%) and piperitenone (31.9%)	2.6	10/98.1			
	M. fruticosa subsp. *serpyllifolia*: linalool (30.3%), pulegone (16.6%) and *p*-menthone (10.3%)	2.4	27/96.7	OM / HD / GC/FID and GC/MS		
	M. fruticosa subsp. *brachycalyx*: linalool (39.9%) and piperitenone (31.9%)	2.6	10/98.1			
	pulegone (56.6-62.9%), *iso*-menthone (15.2-19.3%) and piperitenone (7.1-10.3%) [x]	4.63-4.88	>20/97.9-99.8	OM / HD / GC and GC/MS	Above ground parts/ Turkey	(Arslan, 2012
	pulegone (58.5%), *neo iso*-menthol (8.7%), iso-menthone (3.9%) and (*E*)-caryophyllene (3.9%), para-mentha-3,8-diene (3.7%), *iso*-menthol (3.3%) and isopulegone (3.2%) [y]	2.2	35/87.4	OM / HD / GC/MS	Aerial parts/ Palestine	(Shehab and Abu-Gharbieh, 2012)
	Nablus sample: pulegone (82.9%) and isomenthone (3.2%) [z]	0.67	7/90.5	OM / HD / GC and GC/MS	Aerial parts/ Palestine	(Salameh et al., 2018)
	Ramallah sample: pulegone (86.0%) and isomenthone (3.8%) [z]	0.99	7/94.4			
	Hebron sample: pulegone (74.4%) and isomenthone (14.4%) [z]	0.7	7/93.6			
M. fruticulosa (Bertol.) Šilic	γ-terpinene (14.5%), β-caryophyllene (12.6%), *p*-cymene (8.9%), α-pinene (8.2%) and β-bisabolene (7.2%)	1.6	61/91.3	MH / HD / GC and GC/MS	Aerial parts/ Italy	(Formisano et al., 2007)
	pinocarvone (17.6%), borneol (11.2%), α-bisabolol (10.5%), caryophyllene oxide (4.6%) and linalool (4.5%)	0.1	64/90.1	OM / HD / GC and GC/MS	Aerial parts/ Croatia	(Ruscic et al., 2017)
M. graeca (L.) Bentham et Reichenb.	Sample A: From Attiki Mt Parnes Region: caryophyllene oxide (17.0%), *epi*-α-bisabolol (12.8%), *trans*-verbenol (10.4%) and linalool (9.0%)	0.58	62/92.0	OM / HD / GC and GC/MS	Aerial parts/ Greece	(Tzakou and Couladis, 2001)
	Sample B: From Mt Penteli Region: linalool (18.1%), β-chamigrene (12.5%), *trans*-verbenol (8.3%), germacrene D (7.5%), caryophyllene oxide (7.1%) and epi-α-bisabolol (5.6%)	0.23	62/86.6			
	Vis locality: α-bisabolol (13.9%), camphor (8.1%), *trans*-linalool oxide (6.8%) and allo-aromadendrene (5.2%)	0.5	53/92	OM / HD / GC and GC/MS	Aerial parts/ Croatia	(Vuko et al., 2012)
	Komiža locality: α-bisabolol (15.5%), caryophyllene oxide (7.4%), germacrene D (5.3%) and spathulenol (5.2%)	0.6	51/86.4	OS / HD / GC and GC/ MS		

Table 2 Continued

Plant name (s)	Main components (%)	VOY [a]	Number of identified compounds/ Total percentage	Dominant group/ Extraction method (s)/ Characterization methods (s)	Part(s)/Country	Ref.
M. hedgei Rech. f.	Wild sample: geranial (18.0%), neral (13.8%), geraniol (13.2%), nerol (7.7%), (*E*)-caryophyllene (6.5%), carvacrol (6.2%), geranyl acetate (5.8%), caryophyllene oxide (3.9%), thymol (3.1%) and α-humulene (3.3%)	1.12	49/99.8	OM / HD / GC and GC/MS	Aerial parts/ Iran	(Alizadeh and Ranjbaran, 2017)
	Cultivated sample: geranial (22.7%), neral (16.0%), geraniol (10.7%), nerol (6.0%), (*E*)-caryophyllene (3.8%), carvacrol (5.3%), geranyl acetate (3.1%), caryophyllene oxide (3.9%), thymol (3.6%) and α-humulene (3.3%)	2.23	46/99.7			
M. herpyllomorpha Webb and Berth.	α-pinene (9.2-9.1%), borneol (5.0-8.8%), *trans*-pinocarveol (3.4-5.0%), myrtenal (2.4-3.4%), dehydrosabinene (3.0-5.4%), *p*-cymene (3.0-3.0%), *p*-mentha-l,5-dien-8-ol (3.0-4.0%), *trans*-verbenol (2.7-5.1%), β-bourbonene (2.6-3.0%) and verbenone (2.5-5.7%) [aa]	0.05	64/87-88.3	OM / HD / GC and GC/MS	Aerial parts/ Spain	(Pérez-Alonso et al., 1996)
M. hyssopifolia Webb and Berth.	borneol (13.7%), α-pinene (8.3%), camphor (5.0%), *p*-mentha-1,5-dien-8-ol (5.0%), p-cymene (4.7%), camphene (4.3%), verbenone (3.6%) and *p*-cymen-8-ol (3.0%)	0.15	63/92.8	OM / HD / GC and GC/MS	Aerial parts/ Spain	(Pérez-Alonso et al., 1996)
M. inodora (Desf.) Benth.	*trans*-sesquisabinene hydrate (20.9%), α-terpinyl acetate (19.8%), globulol (4.9%), caryophyllene oxide (4.3%), β-bisabolol (2.9%) and *trans*-7-*epi*-sesquisabinene hydrate (2.6%) [ab]	0.15-0.8	83/94.7	OM / HD / GC-FID, GC/MS and 13C-NMR	Aerial parts/ Algeria	(Benomari et al., 2016)
M. juliana L. Bentham ex Reichenb.	**BFS** [ac]: α-pinene (7.2%), β-pinene (4.9%), linalool (4.7%), borneol (3.5%), *cis*-linalool oxide (2.7%), β-caryophyllene (2.5%), limonene (2.5%), β-cubebene (2.4%), α-gurjunene (2.1%), and *trans*-linalool oxide (1.9%)	0.07	60/65.3	OM / SHE [ae] / GC/MS and TLC	Whole plant/ Croatia	(Mastelić et al., 2005)
	FFS [ad]: α-pinene (10.6%), linalool (7.6%), β-pinene (7.0%), α-gurjunene (6.4%), β-caryophyllene (4.2%), borneol (2.2%), *trans*-linalool oxide (2.0%) and *cis*-linalool oxide (1.5%)	0.11	60/72.0			
	caryophyllene oxide (15.9-20.4%), carvacrol (tr [af]-18.1%), *o*-cymene (0-10.8%), isomenthone (tr-10.1%), pulegone (tr-8.1%), thymol (tr-7.3%), borneol (tr-6.3%), (*E*)-caryophyllene (3.7-7.1%), *allo*-aromadendrene (3.5-5.3%), α-cadinol (1.9-6.6%), *epi*-α-muralol (1.6-3.9%), spathulenol (tr-1.5%), 1-*nor* bourbonanone (1.4-2.2%) and hexahydrofarnesyl acetone (1.2-2.6%)	NR	44-47/84.5-94.8	OS / HD / GC and GC/MS	Aerial parts/ Serbia and Motenegro	(Slavkovska et al., 2005)
	verbenol (11.8%), thymol (10.8%), caryophyllene oxide (10.5%), borneol (9.3%) and myrtenal (7.1%)	0.1	24/87.3	OM / HD / GC and GC-MS	Aerial parts/ Serbia	(Stojanović et al., 2006)
	borneol (9.3%), isomeric verbenols (8.7%) and furanoid linalool oxides (6.5%)	0.1	111/97.9	OM / HD / GC and GC/MS	Aerial parts/ Montenegro	(Palić et al., 2010)
	caryophyllene oxide (10.1-23.3%), piperitoneoxide (2.2-16.9%), (*E*)-caryophyllene (5.2-11.4%), linalool (4.5-7.8%) and β-pinene (3.2-7.0%) [ag]	0.07-0.09	37-49/80.9-95.7	OM, OS / HD / GC and GC/MS	Aerial parts/ Croatia, Bosnia and Herzegovina, Montenegro, Republic of Macedonia and Greece	(Kremer et al., 2014a)
M. kerneri Murb.	caryophyllene oxide (11.7-39.2%), β-pinene (6.3-12.1%), terpinen-4-ol (2.3-3.3%), (*E*)-caryophyllene (2.9-6.9%) and borneol (0.9-6.2%) [ah]	0.05-0.06	54-64/96.0-98.8	OM, OS / HD / GC and GC/MS	Aerial parts/ Croatia	(Kremer et al., 2014a)

Table 2 Continued

Plant name (s)	Main components (%)	VOY [a]	Number of identified compounds/ Total percentage	Dominant group/ Extraction method (s)/ Characterization methods (s)	Part(s)/Country	Ref.
M. kosaninii Šilic	isomeric verbenols (11.7%), furanoid linalool oxides (9.8%) and borneol (8.2%)	0.1	124/96.0	OM / HD / GC and GC/MS	Aerial parts/ Former Yugoslavian Republic of Macedonia	(Palić et al., 2010)
M. lachnophylla Webb and Berth.	borneol (22.0%), bornyl acetate (16.9%), camphene (10.0%), camphor (9.4%), verbenone (3.6%) and α-pinene (3.3%)	0.14	63/91.0	OM / HD / GC and GC/MS	Aerial parts/ Spain	(Pérez-Alonso et al., 1996)
M. lasiophylla Webb and Berth.	porneol (24.9%), linalool (10.9%), camphor (8.6%), camphene (6.1%), α-pinene (4.4%), β-caryophyllene (3.3%) and β-caryophyllene oxide (3.2%) ai	0.14	64/94.3	OM / HD / GC and GC/MS	Aerial parts/ Spain	(Pérez-Alonso et al., 1996)
M. libanotica Boiss.	isomenthone (44.5%), pulegone (13.5%) and isopulegone (6.5%)	1.1	24/83	OM / SD / GC and GC/MS	Leaves and twigs/ Lebanon	(Diab et al., 2005)
M. longipedunculata Bräuchler	Cijevna canyon (CC) region: spathulenol (33.1%), piperitone (8.1%) and piperitone oxide (7.7%)	0.2	43/82.6	OS / HD / GC and GC/MS	Aerial parts/ Montenegro	(Kremer et al., 2014b)
	Mount Krivošija (MK) region: spathulenol (35.9%), piperitone oxide (12.1%) and piperitone (8.9%)	0.2	40/86.3			
	Nikšić (Ni) region: spathulenol (39.5%), piperitone oxide (9.7%) and piperitone (7.3%)	0.3	42/86.2			
	Jazina (Ja) region: spathulenol (30.3%), piperitone oxide (8.9%) and piperitone (8.6%)	0.2	45/89.2	OM, OS / HD / GC and GC/MS	Aerial parts/ Bosnia and Herzegovina	
M. myrtifolia Boiss. Et Hohen	β-caryophyllene (42.6%), germacrene D (7.0%), δ-cadinene (7.0%) and α-humulene (3.0%)	0.03	46/83	SH / HD / GC and GC/MS	Aerial parts/ Turkey	(Özek et al., 1992)
	β-caryophyllene (15.5%), caryophyllene oxide (14.8%), hexadecanoic acid (10.8%), caryophylla-3,8(13)-dien-5β-ol (5.5%) and germacrene D (4.9%)	0.31	62/93.8	SH / HD / GC and GC/MS	Aerial parts/ Lebanon	(Formisano et al., 2014)
M. nubigena H.B.K.	thymol (36.9%), carvacrol (16.7%), pulegone (10.8%), caryophyllene oxide (4.6%) and (E)-phytol (3.2%)	0.91	30/89.7	OM / HD / GC/FID and GC/MS	Leaves and flowers/ Ecuador	(El-Seedi et al., 2008)
	BGTAPR [aj]: (Z)-3-hexenol (31.2%), (Z)-2-hexenol (18.3%) and δ-cadinene (3.4%)		3/52.9	NH [ak]/ HD / GC/FID and GC/MS		
M. parviflora (Vis.) Re-incheb.	limonene (tr af-1.3%), p-cymene (tr-14.6%), linalool (tr-14.3%), thymol (tr-10.6%), isomenthone (0-7.9%), spathulenol (12.7-46.7%), hexahydrofarnesyl acetone (1.9-5.0%) al	NR	28-30/45.9-83.6	OS, OM / HD / GC and GC/MS	Aerial parts/ Serbia and Motenegro	(Slavkovska et al., 2005)
	spathulenol (29.9%), β-bourbonene (7.5%), hexadecanoic acid (5.6%), pentadecanoic acid (4.2%), caryophyllene oxide (3.8%), hexahydrofarnesyl acetone (3.2%), bicyclogermacrene (2.4%), germacrene D (2.2%) and humulene epoxide II (2.0%)	0.1	143/97.5	OS / HD / GC and GC/MS	Aerial parts/ Montenegro	(Palić et al., 2010)
M. persica Boiss.	**BFS** [ac]: thymol (33.1%), γ-terpinene (28.7%), 1,8-cineole (14.2%), *p*-cymene (7.0%) and limonene (5.0%)	3	29/97.2	MH / HD / GC and GC/MS	Aerial parts/ Iran	(Sefidkon and Kalvandi, 2005)
	FFS [ad]: thymol (28.6%), limonene (20.7%), γ-terpinene (17.5%) and *p*-cymene (17.5%)	3.2	34/98.2			
	linalool (15.2%), α-pinene (15.0%) and (*E*)-nerolidol (13.8%)	0.8	24/96.1	OM / HD / GC and GC/MS	Aerial parts/ Iran	(Masoudi et al., 2009)
	n-hexadecanoic acid (14.9%), thymol (9.5%), linoleic acid (8.0%), carvacrol (5.6%), (*E*)-nerolidol (5.5%), linolenic acid (5.5%), α-cadinol (2.7%), linalool (2.7%), borneol (2.6%), caryophyllene oxide (2.3%) and pulegone (2.0%)	0.29	52/88.5	NH: FA am / HD / GC and GC/MS	Aerial parts/ Iran	(Jafari et al., 2018)

Table 2 Continued

Plant name (s)	Main components (%)		VOY [a]	Number of identified compounds/ Total percentage	Dominant group/ Extraction method (s)/ Characterization methods (s)	Part(s)/Country	Ref.
M. pseudocroatica Šilić	Pijavičino (Pi) locality: borneol (22.7%), camphor (16.1%), β-caryophyllene (11.9%) and caryophyllene oxide (9.3%)		0.3	42/86.4	OM / HD / GC and GC/MS	Aerial parts/ Croatia	(Kremer et al., 2012)
	Prapatno (Pr) locality: borneol (24.8%), β-caryophyllene (17.8%), and camphor (13.9%) and caryophyllene oxide (7.4%)		0.2	47/90.4			
M. pulegium (Rochel) Benth.	isomenthone (27.2%), piperitone oxide (7.4%), limonene (6.8%), pulegone (4.0%), piperitenone oxide (3.6%) and piperitenone (1.2%)		NR	47/95.1	OM / HD / GC and GC/MS	Aerial parts/ Serbia and Motenegro	(Slavkovska et al., 2005)
	Wild-growing: pulegone (60.1%) and menthone (26.9%)		0.47	12/98.2	OM / HD / GC and GC/MS	Aerial parts (shoots)/ Serbia	(Stojičić et al., 2016)
	M.P. [an]:	**PG-PGRFM** [ao]: pulegone (44.6%) and menthone (29.2%)	NR	16/98.2			
		PGMSBA [ap]: pulegone (50.8%) and menthone (14.4%)		17/96.1			
M. sinaica Benth.	isoeugenol (31.5%), azulene (10.1%), α-bergamotene (10.0%), β-cubebene (6.1%) and β-linalool (5.5%)		0.5	56/98.0	NH, SH / SD aq / GC and GC/MS	Aerial parts/ Saudi Arabia	(El-Hawary et al., 1991)
M. teneriffae Benth.	α-pinene (20.3%), borneol (14.9%), nerolidol (10.9%), limonene (5.6%) and camphene (4.7%)		0.3	22/88.7	MH ar / HD / GC-FID and IR	Above-ground plant/ Canada as	(Lawrence, 1989)
M. thymifolia (Scop.) Fritsch	piperitenone oxide, pulegone and piperitone at		0 . 3 - 0.5	NA [au]	OM / HD / GC and GC/MS	Aerial parts/ Croatia	(Vladimir-Knežević et al., 2001)
	pulegone (32.8%), piperitenone (25.7%), piperitone (11.7%) and isomenthone (5.0%)		0.99	12/84.4	OM / HD / GC and GC/MS	Leaves/ Yugoslavia	(Marinković et al., 2002)
	pulegone (tr-72.3%), piperitone oxide (0-63.8%), piperitenone (0.4-28.7%), piperitone (0-24.0%), piperitenone oxide (2.4-16.0%), limonene (3.0-11.7%), isomenthone (tr-8.3%) and spathulenol (1.1-2.3%) [av]		NR	32-37/98.4-99.0	OM / HD / GC and GC/MS	Aerial parts/ Serbia and Motenegro	(Slavkovska et al., 2005)
	pulegone (50.4%), piperitenone (10.3%) and piperitenone oxide (4.3%)		1.3	21/78.2	OM / HD / GC and GC/MS	Aerial parts/ Montenegro	(Šavikin et al., 2010)
	piperitone epoxide (38.9%), piperitenone epoxide (28.4%) and limonene (20.8%)		1.3	30/99.1	OM / HD / GC and GC/MS	Aerial parts/ Serbia	(Bukvički et al., 2016)
M. varia Benth. [aw]	α-pinene (20.0-35.0%), geranial (16.0%) and *trans*-nerolidol (15.0%) [ax]		0.3	40-47/90-96	MH /DELN-HD [ay] / GC and GC/MS	Aerial parts/ Portugal	(Pedro et al., 1995)
	borneol (19.2%), α-pinene (13.9%), (*E*) -nerolidol (13.1%), camphene (4.2%), α-terpineol (3.6%) and camphor (3.4%)		0.45	64/95.1	OM / HD / GC and GC/MS	Aerial parts/ Spain	(Pérez-Alonso et al., 1996)

[a] VOY: Volatile oil yield; [b] OM: Oxygenated monoterpenes; [c] HD: Hydrodistillation; [d] NR: Not reported; [e] CSD: Clevenger steam distillation; [f] subsp. *arabica* K. Walth; [g] var. *pilosiuscula* Gray; [h] CC: Column Chromatography; [i] SH: Sesquiterpene hydrocarbons; [j] subsp. *phrygia*; [k] OS: Oxygenated sesquiterpene; [l] W.G.P.: Wild-growing plants; [m] MPM: Micropropagated plant material; [n] GWPGR: Grown without PGRs; [o] SWK: Supplemented with 0.3 µM kinetin; [p] Thirteen populations of *M. dalmatica*; [q] subsp. *amana* (Rech. fil) P.H.Davis; [r] Two sampling areas: Mt. Carmel and Wadi Ara, USA; [s] subsp. *brachycalyx* P. H. Davis; [t] subsp. *serpyllifolia* (Bieb.) P. H. Davis; [u] subsp. *barbata* (Boiss & Kotschy) P. H. Davis; [v] subsp. *giresunica* P.H. Davis; [w] subsp *serpyllifolia*; [x] Grown in 15-35 cm intra-raw spacing (2008-2009); [y] subsp *serpyllifolia*; [z] subsp. *serpyllifolia* (M. Bieb.); [aa] Two samples: *M. herpyllomorpha* Webb and Berth.; [ab] A "collective oil sample": From 24 locations widespread in the littoral of Tlemcen Department, Algeria; [ac] BFS: Before flowering stage; [ad] FFS: Full flowering stage; [ae] SHE: Simultaneous hydrodistillation-extraction; [af] tr: Trace; [ag] For six samples of *M. juliana* (L.) Benth.; [ah] For four samples of *M. juliana* (L.) Benth.; [ai] subsp. *palrnensis* (Bolle); [aj] BGTAPR: β-Glucosidase treatment of the aqueous plant residue; [ak] NH: Non-terpene hydrocarbons; [al] For three samples in Moraca canyon, Cijevna canyon and Rijeka Crnojevica regions, respectively; [am] FA: Fatty acids; [an] M.P.: Micropropagated plants; [ao] PG-PGRFM: Plants grown on PGR-free medium:; [ap] PGMSBA: Plants grown on medium supplemented with 10 µM N^6-benzyladenine (BA); [aq] SD: Steam distillation; [ar] MH: Monetrerpene hydrocarbons; [as] From seeds of Tenerife B. G. Canary Islands origin; [at] The full detail was unavailable; [au] NA: Not available; [av] For five samples in Derventa canyon, Beli Rzav gorge, Moraca canyon, Semolj and Mt Orjen regions, respectively; [aw] subsp. *thymoides* (Sol. ex Lowe) Pérez var. *thymoides*; [ax] For vegetative phase and the flowering period, respectively; [ay] DELN-HD: Distillation-extraction, for 3 h, using a Likens Nickerson-type apparatus in combination of HD.

for the production of EOs components and, therefore, could be applied as promoters to obtain EOs enriched in specific components. On the other hand, screening of the chemical profiles of the EO samples of *M. croatica* (Pers.) Schott which were supplemented with 0.3 μM kinetin led to the characterization of high quantities of oxygenated monoterpenes with geranial as the dominant compound, as well.

2.2. Phytochemistry

The *Micromeria* species have been mainly investigated for the essential oil composition, which has been discussed in the previous section. There are only a few reports in the literature concerning the more polar phytochemicals incuding low or less volatile metabolites. Among these, some papers have reported the isolation of a few not previously described compounds, whose structures are reported in Fig. 1. The glycosidic flavonoid acacetin 7-*O*-[6‴-*O*-acetylglucosyl(1‴→2″)] rhamnosyl(1‴→6″)glucoside (**1**) originally identified in a taxonomically related species, *Calamintha glandulosa* (Marin et al., 2001), has been also characterized in several *Micromeria* species. In the majority of the cases, *e.g.*, *M. dalmatica* Benth., *M. thymifolia* (Scop.) Fritsch and *M. albanica* (Gris. ex K. Maly) Silic, it appeared as the most abundant flavonoid, while in other cases like *M. juliana* (L.) Benth. ex Reich. and *M. cristata* (Hampe) Grisebach, it has been reported as a minor one. The restricted occurrence of compound (**1**) and the structurally related 7-*O*-rhamnosyl(1‴→6″)glucoside (**2**) in systematically close species belonging to the genera *Satureja*, *Acinos* and *Clinopodium* indicates that their distribution is of taxonomic relevance (Marin et al., 2001). Piperitone 7-*O*-β-D-glucoside (**3**) and isothymonin 4′-methyl ether (**4**), were isolated from an acetone extract of *M. cilicica* (Öztürk et al., 2011), together with other components of flavonoid, phenolic, triterpenoid and saccharidic nature, involving sudachitin, isomucronulatol, rutin, ursolic acid, carvacrol, thymol, α-tocopherol and saccharose. An oleanane ester with palmitic acid, namely 3β-palmitoyloxyolean-11:13(18)-diene (**5**) was identified in *M. persica* Boiss. (Kalaki Kordkolaei et al., 2019), together with other phenolic and terpenoidal compounds, *e.g.*, bongardol, linarin, betulinic acid, ursolic acid, daucosterol and β-sitosterol. The fractionation of the acetone extract obtained from *M. nervosa* (Desf.) Benth. afforded the identification of a furanosesquiterpene alcohol, micromeriol (**6**), and a 5-β-cholestane derivative, trivially named as nervosane (**7**), together with β-sitosterol, oleanolic acid and ursolic acid (Abdelwahab et al., 2015). The phenolic component pattern present in the *Micromeria* genus reflects the classical composition showed by species comprised in the Nepetoideae subfamily, with rosmarinic acid as the principal component in the majority of the cases. This is in accordance with what has been observed in closely related species, such as *Mentha aquatica* (Venditti et al., 2017b). In fact, rosmarinic acid is considered as one of the main chemotaxonomic markers in this plant subfamily. In addition, the presence of caffeoylquinic and dicaffeoylquinic derivatives is consistent with the chemotaxonomy of species comprised in the Nepetoideae subfamily and, more in general, with the Lamiaceae family. Concerning the flavonoids, there are two aspects which deserve to be noted. Te first is the presence of highly oxygenated derivatives (6-OH functionalization, scutellarein related compounds), such as cirsilineol already identified in *Teucrium polium* (Lamiaceae) (Venditti, 2017) and linariin (Kalaki Kordkolaei et al., 2019) recognized in other taxa of the Lamiales such as *Kickxia spuria* subsp. *integrifolia* (Venditti et al., 2018) and *Linaria reflexa* (Cheriet et al., 2014). All of these compounds are of notable chemotaxonomic relevance (Tomás-Barberán et al., 1988; Tomas-Barberan et al., 1991; Marin et al., 2001). The second one is related to the tendency in *Micromeria* to the accumulation of flavonoids in the acetylated diglycosidic form as already observed in other Lamiaceae species such as *Stachys tymphaea*, *S. annua* and *Galeopsis angustifolia* (Venditti et al., 2013e, 2014b, 2015c). A couple of other works on the metabolite pattern of two *Micromeria* species are available in literature. The first one analyzed *M. graeca* (L.) Benth. ex Rchb. extract with an NMR metabolomic approach which revealed the presence of rosmarinic acid as the main phenolic component together with organic acids and primary metabolites (Scognamiglio et al., 2015). Rosmarinic acid has been identified in other Lamiaceae species (Venditti et al., 2015b; Venditti et al., 2016d) and is considered as chemotaxonomic marker in the Nepetoideae subfamily (Pedersen, 2000). The second study was instead conducted on *M. fruticosa* L. by applying an HPLC-DAD-ESI-QTOF-MS^2 analytical approach (Abu-Reidah et al., 2019). The latter method permitted the detection of over 180 phytochemicals consisiting of 87 flavonoids, 41 phenolic acids, 16 terpenoids, 8 sulfate derivatives, 7 iridoids, and others. The tentative identification of seven iridoids should be considered with some criticism. Because, three of them were indicated as deacteylasperuloside isomers, and the others designated as sylvestroside IV dimethyl acetal, scropolioside A, loganic acid and acetylbarlerin. Iridoids are important marker compounds in the Lamiaceae family (Frezza et al., 2019a; Frezza et al., 2019c) and their biogenesis has been extensively studied. It has been observed that iridoids with 8α-stereochemistry are peculiar in the Lamiaceae and in other families in the Lamiales order. The iridoids with 8α-stereochemistry are derived by the biogenetic *Route II*, while the iridoids with 8β-stereochemistry are instead derived by the biogenetic *Route I* and are characteristic metabolites of plant species comprised in different families than Lamiaceae, such as Apocynaceae, Gentianaceae and Rubiaceae (Jensen, 1992). The precursors and intermediate compounds in these two biogenetic *Routes* (*I* and *II*) are different: the *Route I* involves iridodial, loganic acid and loganin, all compounds owning 8β-stereochemistry; the *Route II* involves the *epi*-analogs, *epi*-iridodial, *epi*-loganic acid and *epi*-loganin as biosynthetic intermediates and all are epimers at the 8 position showing the α-stereochemistry (Fig. 2). Considering an analytical method, namely HPLC-DAD-

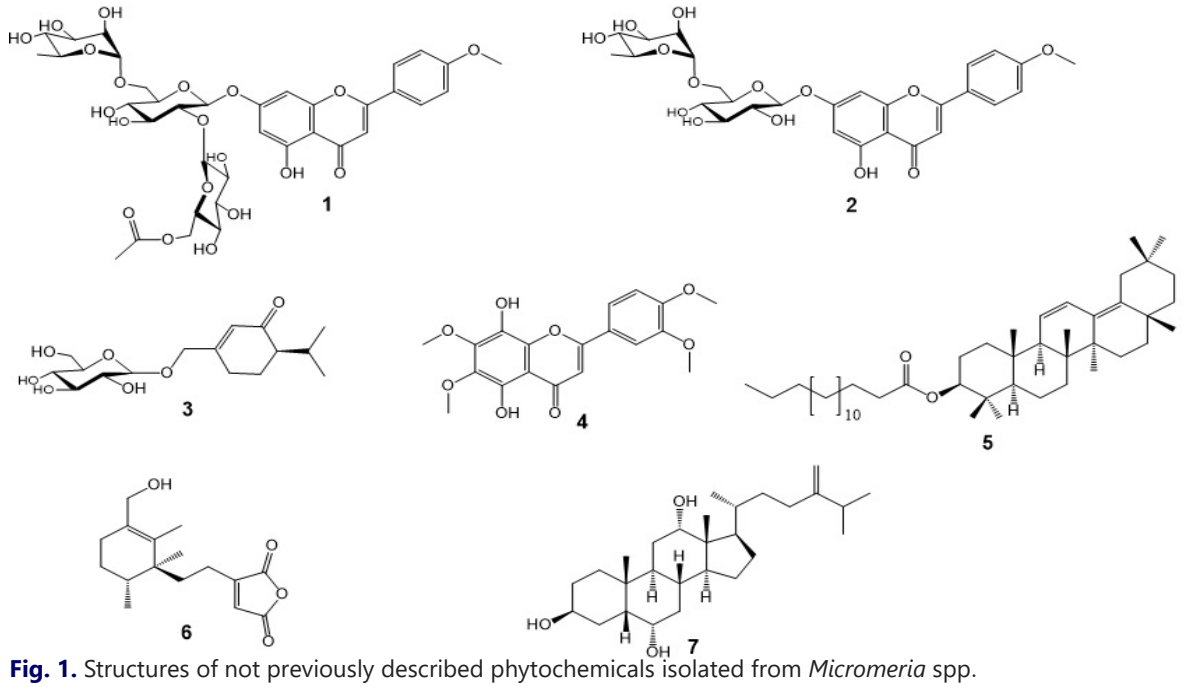


Fig. 1. Structures of not previously described phytochemicals isolated from *Micromeria* spp.

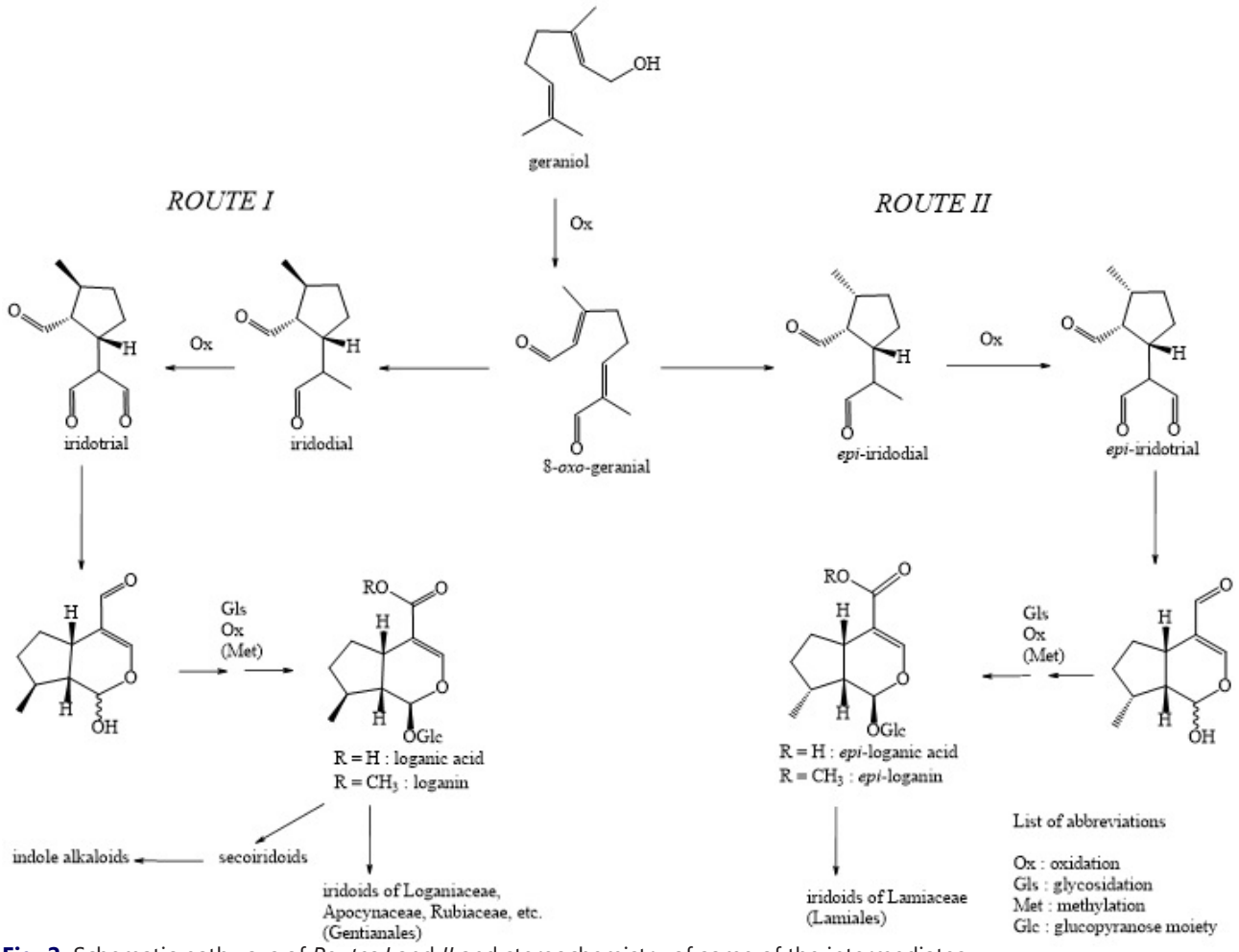


Fig. 2. Schematic pathways of *Routes I* and *II* and stereochemistry of some of the intermediates.

ESI-QTOF-MS^2 applied by Abu-Reidah et al. (2019) in which the tandem MS was used to determine the exact mass of main ions and fragments in case of unavailability of commercial standards, it should be underlined that two iridoids epimer at C-8 may undergo the same kind of fragmentation; therefore, they would not be differentiated. For this reason and considering the biogenesis of iridoids in Lamiaceae derived by the *Route II*, it is much likely that instead of loganic acid, its epimer was really present in *M. fruticosa,* as already observed in other species of the Lamiales order and the Lamiaceae family itself, such as *Galeopsis angustifolia*, *Pedicularis kerneri*, *Hyssopus officinalis* subsp. *aristatus, Sideritis montana* L. subsp. *montana, Scrophularia canina*, *Pedicularis rostratocapitata*, *Odontites luteus* (Jensen, 1992; Venditti et al., 2013d; Venditti et al., 2015b; Venditti et al., 2016a; Venditti et al., 2016c; Venditti et al., 2016e; Venditti et al., 2016f; Venditti et al., 2017c) and several others. Similar considerations from the biogenetic standpoint could be inferred for the presence of sylvestroside IV, a bis-iridoid constituted by two subunits: one cyclopentapyrane ring (iridane) and one seco-iridoid moiety. The former subunit is structurally related to loganin aglycone, while the latter is related to swerosidic acid and both the subunits are derived from *Route I*. In fact, sylvestroside IV was first recognized from *Dipsacus sylvestris* of the Dipsacaceae family (Jensen et al., 1979) together with loganin, sweroside and cantleyoside, all iridoids formerly derived from *Route I*. This is an interesting aspect which deserves further studies because the component really contained in the studied plant species might be one isomer of sylvestroside IV. In this regard, new studies on the stereochemistry are advisable by applying suitable relevant methods. On the other hand, it should be also noted that sylvestroside IV was identified in the dimethyl acetal form which is a possible artifact due to the extraction procedure with methanol (Venditti, 2020). The presence of the *seco*-iridoid subunit should be also confirmed in further studies since this class of metabolites is quite rare in the Lamiales and there are very few reports in literature in this regard. Two derivatives belonging to this class of glycosidic monoterpenoids have been recently recognized in *Pedicularis verticillata*, a species from the Orobanchaceae family formerly comprised in the Scrophulariaceae (Venditti et al., 2016c). Considering the Lamiaceae family, *seco*-iridoid derivatives have been previously observed only in *Lamium album* and it was also proved that they are derived from 8-*epi*-deoxy-loganic acid (Damtoft et al., 1992a; Damtoft et al., 1992b) which is one of the precursors in the biosynthetic *Route II*. The other literature case by Rastrelli et al. (1998) reported on the identification of loganin and biosynthetically derived *seco*-iridoids in *Lippia graveolens* Kunth. (Verbenaceae), thus giving an additional evidence of their extreme rarity in the Lamiales order. Another aspect related to the iridoid content in *M. fruticosa* which deserves a brief discussion is about the presence of the three compounds tentatively identified as deacteylasperuloside isomers. In fact, also the asperuloside analogs are derived from *Route I* and considered to be characteristic of different botanical families such as the Rubiaceae, and in particular for species of the Rubioideae subfamily (Venditti et al., 2014a; Venditti et al., 2015d) even if unexpectedly they have been recently found in *Ajuga chamaepitys* (Venditti et al., 2016b) (Lamiaceae). The presence of components related to the asperuloside is quite strange from the biogenetic standpoint but it cannot completely exclude their real presence in the studied *Micromeria spp.*, in particular if considering that due to the presence of the unsaturation at 7,8 positions of the cyclopentapyrane skeleton of asperuloside related compounds in which the α-configuration at C8 is lost. One possible precursor, in accordance with the biogenetic *Route II,* might be geniposidic acid, one iridoid already recognized, together with other biogenetic markers with the 8α-configuration such as 8-*epi*-loganin, in species comprised in the Lamiales order (Venditti et al., 2013c; Venditti et al., 2015a). In fact, a simple oxidation at C6 position of geniposidic acid could be enough to provide a hydroxyl substituent at this position just like the asperuloside analogs. Furthermore, the functionalization at C6 could be favored by the intrinsic reactivity due to the allylic like conformation. In this context, it should be also considered that in the past asperulosidic acid and asperuloside have been isolated from *Lamium amplexicaule* (Alipieva et al., 2003; Kikuchi et al., 2009), although in another study on the biosynthesis of iridoids using tritium-labeled precursors and conducted in *L. amplexicaule*, *Deutzia crenata*, and *Galium spurium* var. *echinospermon*, the presence of asperuloside has been confirmed only in *G. spurium* (Inouye et al., 1978) which is one species comprised in the Rubiaceae family, while *L. amplexicaule* and *D. crenata*, on the other hand, belong respectively to the Lamiaceae and Hydrangeaceae families. Obviously, all these aspects as well as the presence of iridoids in the genus *Micromeria* deserve further investigation since this genus is comprised in the tribe Mentheae within the Nepetoideae subfamily (Lamiaceae), and the majority of the genera classified in Nepetoideae comprise not or less iridoid-producer species. It should be noted that several authors consider the Lamiaceae family as being splitted into two groups (Wink, 2003; Fraga et al., 2009) based on the different biosynthetic utilization of the common precursor geranyl pyrophosphate: one comprising EOs producer species (aromatic plants) and corresponding to the subfamily Nepetoideae, the other comprising oil-poor species rich in iridoids and belonging to the subfamily Lamioideae. Actually, there are also species which showed the presence of both EO components and iridoids in the Menthae tribe of Nepetoideae [*i.e.*, *Hyssopus officinalis* (Venditti et al., 2015b)] as well as in the Lamioideae [*i.e.*, *Sideritis italica* (Venditti et al., 2013a)] and this should suggest that there is a need for a strict cooperation between phytochemistry and morphology in the classification of plant species because the separation of the two groups might not be clear and several botanical entities of the same genus with intermediate phytochemical patterns

might exist. Concerning the case of these seven (possible) iridoids recognized in *M. fruticosa* L. (Abu-Reidah et al., 2019), it would be desirable that the presence of these compounds will be also confirmed by isolation and determination of their chemical structures with suitable methods, *i.e.*, NMR spectroscopy and mass spectrometry. On the other hand, the composition of volatile metabolites like EOs, was consistent with the general composition observed in the Nepetoideae, which is dominated by high frequency of oxygenated monoterpenes and sesquiterpenes. In particular, it is notable that several *Micromeria* spp. have shown EOs mainly composed of pulegone/piperitone-related compounds (Table 2), while only a few species showed other compounds as main components, *i.e.*, thymol in *M. persica* Boiss., isomenthone in *M. libanotica* Boiss., menthone in *M. frivaldszkyana* (Degen) Velen. and geranial in *M. biflora* (Buch. Ham. ex D. Don) Benth. It is possible that these main constituents could be regarded as chemotaxonomic marker in the respective species, as already observed in the case of menthol and the entities comprised in the *Mentha* genus (Frezza et al., 2019c).

2.3. Ethnobotany, traditional and folkloric uses of different species of the genus *Micromeria*

M. fruticosa (L.). Druce is one of the important *Micromeria* species, which is known as "white micromeria" and has a wide distribution range in some of the Middle East countries including Lebanon, Palestine, Syria, Jordan and Turkey. The aerial parts of this plant, particularly in the Eastern Mediterranean region, are frequently prescribed for the treatment of cold, cough, eye infections, diarrhea, heart and cardiovascular disorders, high blood pressure, faintness as well as abdominal pains. The aerial parts of *M. fruticosa* (L.). can also serve as an effective antiseptic agent in open wounds. The plant can inhibit wheat seed germination (Dudai et al., 1999) and it is an effective insecticidal and acaricidal agent (Çalmaşur et al., 2006). Regarding the pungent and pleasant fragrance of the *Micromeria* plants, different species of this genus are traditionally used as herbal teas and flavoring agents in the preparation of local foods in many parts of Turkey and also as an alternative for mint in the Turkish folk medicine (Kirimer et al., 1993a; Kirimer et al., 1993b; Krimer et al., 1993; Tabanca et al., 2001; Duru et al., 2004). Also, some CNS-stimulant, sedative, expectorant, abortifacient, antiseptic, insecticidal, herbicidal, antibioherbicide, antirheumatic, antiinflammatory and anaesthetic properties have been described (Ali-Shtayeh et al., 1997; Dudai et al., 1999; Güllüce et al., 2004; Formisano et al., 2007; Stojanović and Palić, 2008; Tošić et al., 2019). In the literature, some promising medicinal uses have been reported for some species of this genus, such as its ability to remove kidney stones and as powerful remedies against indigestion, skin burn and infections, cold, stomachache, headache, liver, heart and pulmonary diseases, toothache, eye inflammation along with chest pains in Turkey (Baytop, 1984; Ali-Shtayeh et al., 1997; Kırımer and Baser, 1997; Tabanca et al., 2001). The herbal tea from *M. cilicica* Hausskn. ex P.H. Davis has been suggested as a degasifier and an appetizer (Duru et al., 2004). Moreover, in addition to the main use as a spice, *M. cilicica* Hausskn. ex P.H. Davis and *M. myrtifolia* Boiss. can act as a stimulant in the traditional medicine of the southern parts of Anatolia (Özcan, 1999; Duru et al., 2004). In Turkey, *M. congesta* has been used as tea by the local Turkish people since many years ago (Stojanović and Palić, 2008). In the Spanish traditional medicine, *M. graeca* (L.) Rchb and *M. biflora* Benth. are highly recommended for stomach malfunctions and pains as well as digestive tract disorders. The other members of the genus *Micromeria*, namely *M. herpyllomorpha* Webb and Berth and *M. varia* Bentham are used as capillary tonic agents, in Canary Islands, Spain, as well (Rivera and Obón, 1992). These species have also been recognized as proper remedies against hypertension and to heal bathing inflammed sore eyes (Dudai et al., 2000) In the traditional herbal medicine of Lebanon, the herbal drink prepared from *M. libanotica* Boiss., as an endemic plant, serves as a strong anti-cough drug (Diab et al., 2005). In some of the East European regions, particularly Croatia and neighboring areas, the leaves of *M. juliana* (L.) are used as a food flavoring additive and a diuretic agent (Mastelić et al., 2005). *M. graeca* (L.) Benth. ssp. *graeca* has been used in the Italian folk medicine, in particular in the Basilicata region, southern parts of Italy, for the effective treatment of severe coughs and as a remedy against cold (Guarrera et al., 2005). In addition, in the traditional folk medicine of Bosnia and Herzegovina, it is common to use an infusion from the aerial parts of *M. thymifolia* (Scop.) Fritsch to heal gastrointestinal and lung disorders. Furthermore, the flowers and leaves of this herb have been recommended as powerful remedies against the inflammation of lymphatic nodule and to refine the human body blood (Redžić, 2007). In the traditional medicine of Balkans area, *M. thymifolia* (Scop.) Fritsch has long been used, particularly to treat some disorders related to the central nervous system, namely epilepsy and hysteria (Saric-Kundalic et al., 2011). It has also been shown that this medicinal plant is a good option against abdominal and respiratory malfunctions (Bukvički et al., 2016). In the traditional Chinese medicine, *M. biflora* Benth. has been recommended as an effective beverage for health promotion and an effective remedy to treat gastropathy as well as some other abnormalities in digestive tract (Stojanović and Palić, 2008). Local Chinese people also use this herbal plant for the preparation of arctium lappa pickles. In the Palestinian local medicine, it has been stated that *M. fruticosa serpyllifolia* (M. Bieb.), with a pleasant smell, is capable of decreasing the temperature of the human body. It is also used as an edible plant (Ali-Shtayeh et al., 2008). In addition, some relevant papers have discussed its tonic characteristics and remarkable strength against asthma, hypertension, backache, faintness, skin problems, diabetes, cancer and eye inflammation

in Palestine (Ali-Shtayeh et al., 2008; Yaniv and Dudai, 2014; Salameh et al., 2018; Abu-Reidah et al., 2019). In some African countries like Algeria, a decoction prepared from the aerial parts of different *Micromeria* species can relieve painful stomachache and act as a strong herbal drug against cough, cold and fever. Moreover, it can improve and effectively heal infectious wounds, and its dried parts have been recommended as condiments for culinary purposes (Benomari et al., 2016; Brahmi et al., 2017).

In Ecuador, another *Micromeria* endemic species, namely *M. nubigena* H.B.K., traditionally known as "Sunfillo", has been recognized as a digestive, antidiarrhetic and tonic remedy with interesting healing properties against sunburns (White, 1976).

2.4. Biological activities

2.4.1. Antioxidant activity

The study of the antioxidant properties of plant species appears to be of primary importance to discover compounds with potential applications for human health, not only in nutraceutical and phytopharmaceutical fields, but also in the food industry as food preservatives (Shan et al., 2009). The antioxidant activities of organic extracts and EOs of several *Micromeria* species have been evaluated in some of the previously published papers. In this regard, the data available in the literature have been summarized in Table 3. To assess the antioxidant capability of an EO or of an organic extract, the common used assays involve 1,1-diphenyl-2-picrylhydrazyl radical (DPPH$^{\bullet}$), β-carotene-linoleic acid bleaching assay (BCLBA), 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS$^{\bullet+}$), $O_2^{\bullet-}$ assay ($O_2^{\bullet-}$), OH$^{\bullet}$ scavenging activity (OH$^{\bullet}$SA), ferric reducing/antioxidant power (FRAP) and iron chelating activity (ICA). Using four standard antioxidant assays including BCLBA, DPPH, ABTS$^{\bullet+}$ and $O_2^{\bullet-}$ on some organic extracts of *M. cilicica* Hausskn. ex P.H. Davis, *e.g.*, methanol, acetone and pethroleum ether from the aerial parts of *M. cilicica* Hausskn. ex P.H. Davis, the highest antioxidant activity and the least IC_{50} value was evidenced for the acetone extract (Öztürk et al., 2011). The acetone extract, which showed the best antioxidant activity, was then subjected to chromatographic separations for the identification of its phytochemical composition. From the separation procedure, seven compounds were identified, among which two characterized compounds have not previously been described and were presented in the phytochemistry section. However, the antioxidant capabilities of the other organic extracts showed different bioactivity levels, ranging from the remarkable to medium effectiveness when compared with standard compounds shuch as BHT, tocopherol and quercetin. In a parallel work, the ethanol extract of three species of the genus *Micromeria*, namely *M. croatica* (Pers.) Schott, *M. juliana* (L.) Bentham ex Reichenb and *M. thymifolia* (Scop.) Fritsch were subjected to four antioxidant assays involving DPPH$^{\bullet}$, OH$^{\bullet}$SA, FRAP and ICA. A simple perusal of the obtained results exhibits that the highest antioxidant activity was related to *M. croatica* (Pers.) Schott using the DPPH$^{\bullet}$ assay, with an IC_{50} of 4.67 µg/mL. Furthermore, the total antioxidant capability of the ethanol extracts was found to be, respectively, 470.03, 284.5 and 265.8 in terms of equivalents of ascorbic acid (mg AAE/g) (Vladimir-Kneževic et al., 2011). Brahmi et al. (2017) determined the antioxidant activity of the ethanol fraction of the hexane extract of *M. graeca* (L.) Benth. ex Rchb. by using four assays (DPPH$^{\bullet}$, BCLBA, ABTS$^{\bullet+}$ and $O_2^{\bullet-}$). The IC_{50} values obtained using the DPPH$^{\bullet}$, BCLBA, ABTS$^{\bullet+}$ (Table 3) were found to be, respectively, 65.8, 23.4 and 30.5 µg/mL. In addition, using the $O_2^{\bullet-}$ assay, antioxidant index values of AI_{30} and AI_{50} for this extract were reported to be, respectively, 332 and 638 µg/mL. These indices values respectively account for the amount of extract required for scavenging 30% or 50% of the electrogenerated radicals present in the reaction medium. The most active natural plant-derived antioxidants have a polyphenolic nature and also this class of metabolites has been observed in species of the *Micromeria* genus, *i.e.*, apigenin, a well-known flavonoid with antioxidant and many other health promoting activities (Salehi et al., 2019). All these polyphenols are likely implicated in the observed antioxidant activity.

2.4.2. Antibacterial activity

The plant materials represent an important source of metabolites with specialized functions that can be explored with the aim of identifying new active molecules. The plant kingdom is vast and, in many cases, largely unexplored from the phytochemical and biological activity points of view, so it is auspicable that in the future, studies on these aspects will increase. In this section, the results of antibacterial activity from *Micromeria* spp. are summarized and discussed. Indeed, among diverse biological activities of different EOs or organic extracts, antibacterial assessments are of paramount interest. Similar to many other herbal species, EOs and extracts of different *Micromeria* species have shown efficient inhibition against a wide range of bacterial strains and their response toward different bacteria can be interpreted in terms of inhibition zone diameter (IZD), minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). A summary of the reports discussing antibacterial-based measurements on *Micromeria* plants during the recent years is displayed in Table 4. However, as different groups used different antimicrobial assays and also results were reported using various units of concentrations, it is somewhat impossible to have a proper comparative insight into the potential antimicrobial properties of some of the species of this genus. In this regard, it could be useful to follow the guidelines proposed by Cos and coworkers (2006). Summarizing, the highest IZD of EOs of *M. thymifolia* (Scop.) Fritsch, *M. albanica* (Griseb. ex K. Maly) Silic and *M. dalmatica* Benth. toward *M. luteus*, *M. luteus* and *B. subtilis* were observed, respectively, as 26-36, 22-30 and 18-25 mm over a range of 1-10 µL of each EO volume (Marinković et al.,

Table 3
Antioxidant activities of diverse essential oils and extracts of *Micromeria* genus.

Sample		Plant name	Plant organ	Antioxidant assay/Standard method	Antioxidant activity				Ref.
					IC_{50}	RSA(%) [a]	Versus to standard: Amount	TAA [b]	
Extract		*M. graeca* (L.) Bentham ex Reinchenb.	Aerial parts	Umezawa method	NR [c]	NR	α-Tocopherol: 0.98	-	(Couladis et al., 2003)
		M. juliana (L.) Bentham ex Reinchenb.					α-Tocopherol: 0.86		
EO*		*M. fruticosa* ssp *serpyllifolia*	Aerial parts	DPPH [d]	9802	NR	-	-	(Güllüce et al., 2004)
Extract				BCLBA [e]	NR	21.6			
				DPPH•	70.9	NR			
				BCLBA	NR	59			
Extracts		*M. juliana* (L.) Bentham ex Reinchenb.	Aerial parts	DPPH•, BCLBA	NR, NR	NR	α-Tocopherol, BHT	Extracts	(Öztürk et al., 2009)
							α-Tocopherol, BHT		
Extract	DEE [f]	*M. cristata* L.	Aerial parts	DPPH•	50 mg/mL	-	-	-	(Panovska and Kulevanova, 2010)
				Fe^{3+}/ascorbate/ EDTA/H_2O_2	-	52			
	EtOAc [g]			DPPH•	40 mg/mL	-			
				Fe^{3+}/ascorbate/ EDTA/H_2O_2	-	57			
	BuOH [h]			DPPH•	20 mg/mL	-			
				Fe^{3+}/ascorbate/ EDTA/H_2O_2	-	47			
Extract		*M. thymifolia* (Scop.) Fritsch	Whole plant	DPPH•	-	6.5	-	-	(Lin et al., 2011)
Extract	PE [i]	*M. cilicica* Hausskn. ex P.H. Davis		BCLBA	35.4 µg/mL	-	-	-	(Öztürk et al., 2011)
				DPPH•	>200 µg/mL				
				$ABTS^{•+}$ [o]	97.1 µg/mL				
				$O^{•-}_2$ [p]	NA				
	AC [j]			BCLBA	7.68 µg/mL				
				DPPH•	70.8 µg/mL				
				$ABTS^{•+}$	30.2 µg/mL				
				$O•^-_2$	150 µg/mL				
	Fr. MCA 11 [k]			BCLBA	NT				
				DPPH•	76.8 µg/mL				
				$ABTS^{•+}$	NT				
				$O^{•-}_2$	NT				
	Fr. MCA 36-40 [l]			BCLBA	NT				
				DPPH•	25.1 µg/mL				
				$ABTS^{•+}$	NT				
				$O^{•-}_2$	NT				
	Fr. MCA 54 [m]			BCLBA	NT				
				DPPH•	28.0 µg/mL				
				$ABTS^{•+}$	NT				
				$O^{•-}_2$	NT				
	MeOH [n]			BCLBA	27.1 µg/mL				
				DPPH•	74.7 µg/mL				
				$ABTS^{•+}$	37.1 µg/mL				
				$O^{•-}_2$	137 µg/mL				

Table 3 Continued

Sample		Plant name	Plant organ	Antioxidant assay/Standard method	Antioxidant activity				Ref.
					IC_{50}	RSA(%) [a]	Versus to standard: Amount	TAA [b]	
Extract		*M. croatica* (Pers.) Schott	Aerial parts	DPPH•	4.67 µg/mL	-	-	470.03	(Vladimir-Kneževic et al., 2011)
				OH•SA [q]	249.65 µg/mL				
				FRAP [r]	9.64 µg/mL				
				ICA [s]	227.47 µg/mL				
		M. juliana (L.) Bentham ex Reichenb		DPPH•	7.95 µg/mL				
				OH•SA	324.03 µg/mL				
				FRAP	12.38 µg/mL			284.5	
				ICA	254.33 µg/mL				
		M. thymifolia (Scop.) Fritsch		DPPH•	8.33 µg/mL				
				OH.SA	390.98 µg/mL				
				FRAP	17.64 µg/mL			265.76	
				ICA	336.33 µg/mL				
EO		*M. myrtifolia* Boiss. & Hohen.	Aerial parts	DPPH•	-	-	Trolox Equivalents: mmol/L	0.05	(Formisano et al., 2014)
				FRAP		-		0.8	
Extract	HE [t]			DPPH•				0.02	
				FRAP				0.75	
	CE [u]			DPPH•				0.22	
				FRAP				0.48	
	MeOH			DPPH•				1.35	
				FRAP				2.43	
Extract	MeOH	*M. fruticosa* (L)	Whole plant	DPPH•	-	98.5	-	-	(Abu-Gharbieh and Ahmed, 2016)
	EtOH v					97.5			
	EtOAC					98.3			
	AC					98.1			
Extract	WE [w]	*M. biflora* Buch. Ham. ex D. Don	Whole plant	DPPH•	-	71	-	-	(Uddin et al., 2016)
	MeOH					80.3			
Extract	HE-EtOH	*M. graeca* (L.) Benth. ex Rchb.	Aerial parts	DPPH•	65.8 µg/mL	NR	-	-	(Brahmi et al., 2017)
				BCLBA	23.4 µg/mL				
				$ABTS^{\bullet+}$	30.5 µg/mL				

*EO: Essential oil; [a] RSA: Radical Scavenging Activity; [b] TAA: Total Antioxidant Activity; [c] NR: Not reported; [d] DPPH: 1,1-Diphenyl-2-picrylhydrazyl radical; [e] BCLBA: β-Carotene-linoleic acid bleaching assay; [f] DEE: Diethyl ether; [g] EtOAC: Ethyl acetate; [h] BuOH: *n*-Butanol; [i] PE: Petroleum ether; [j] AC: Acetone; [k] Fr. MCA 11: fraction involving thymol, carvacrol, two unidentified compounds along with vitamin E (α-tocopherol); [l] Fr. MCA 36-40: being eluted with a mixture of hexane, chloroform and methanol (7:4:1, v/v/v); [m] Fr. MCA 54: Being eluted using methanol on a Sephadex LH-20 column to produce nine sub-fractions namely MCA 54 (1-9); [n] MeOH: Methanol; [o] $ABTS^{\bullet+}$: 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); [p] $O^{\bullet}_2$: $O^{\bullet}_2$ assay; [q] OH•SA: OH• scavenging activity; [r] FRAP: Ferric reducing/antioxidant power; [s] ICA: Iron chelating activity; [t] HE: Hexane extract; [u] CE: Chloroform extract; [v] EtOH: Ethanol; [w] WE: Water extract

2002). Unfortunately, in this study, only negative control was performed and the antibacterial effectiveness of the EO cannot be compared with those of a standard antimicrobial drug so as to also check if the EO is more or less effective than the drugs currently in use. The activity of *M. cilicica* Hausskn. ex P.H.Davis oils obtained using water-based distillation (HD), steam distillation (SD) along with their main constituent, pulegone, as well as the organic extracts of this plant using hexane, chloroform and ethyl acetate as solvents have been separately evaluated against nine bacterial strains. A medium level of activity was noted in most cases. However, pulegone showed maximal IZD (22-23 mm) vs. *S. typhimurium* and the second rank was due to EO obtained using SD approach toward *S. aureus* (17-22 mm). Moreover, negligible to medium activities were reported for EOs and extracts of some of the other *Micromeria* species, namely *M. fruticosa* ssp *serpyllifolia* (Güllüce et al., 2004), *M. nubigena* H.B.K. (El-Seedi et al., 2008), *M. inodora* (Desf.) Benth. (Benomari et al., 2016) and *M. graeca* (L.) Benth. ex Rchb. (Brahmi et al., 2017) against some sets of Gram (+) and Gram (-) bacteria. Interestingly, the EO obtained from *M. nubigena* showed a high percentage of thymol which was characterized as the main component constituting about 37% of the whole composition (El-

Seedi et al., 2008). This compound is known to exert antimicrobial activity and its presence in the oil is directly correlable to the observed activity. In fact, the distillate obtained after eliminating the traces of volatile components of the plant material already subjected to hydrodistillation and treated with glucosidase to release any volatile compounds present in the form of glycosides has been proved to be completely inactive toward all the microorganisms tested and thymol was absent in its chemical composition. On the other hand, the ethanol extract obtained from *M. graeca* resulted to be inactive as an antimicrobial agent but showed the capability to restore the efficacy of antibiotics on multi-resistant strains (Brahmi et al., 2017) and this aspect deserves further investigations. Dulger (2008) has determined the antibacterial potential of methanol and chloroform extracts of *M. cilicica* Hausskn. ex P.H.Davis, *M. dolichodontha* P.H. Davis and *M. cremnophila* subsp. *amana* against *S. aureus*, *S. sanguis*, *E. coli*, *P. aeruginosa* and *K. pneumoniae* following their numerical IZD and MIC values (Table 4). For methanol extracts, the best antibacterial results for *M. cilicica* Hausskn. ex P.H.Davis, *M. dolichodontha* P.H. Davis and *M. cremnophila* subsp. *amana* were, respectively, observed vs. *S. sanguis* (IZD = 10.4-15.8 mm; MIC=25 mg/mL); *P. aeruginosa* (IZD = 8.2-11 mm; MIC = 40 mg/mL) and *K. pneumoniae* (IZD = 9.6-16.6 mm; MIC=10 mg/mL). Additionally, for the $CHCl_3$ extracts of the above-mentioned plants, the most remarkable antibacterial potency was respectively attributed to *S. sanguis* (IZD = 10.8-18.8 mm; MIC = 10 mg/mL), *P. aeruginosa* (IZD = 8.8-13.8 mm; MIC = 25 mg/mL) and *P. aeruginosa* (IZD = 11.8-18.4 mm; MIC = 1.0 mg/mL). Over a concentration range of 10-1000 µg/disk and versus eleven bacterial strains, the EOs of *M. congesta* Boiss. & Hausskn. ex Boiss. exhibited a satisfactory inhibition, in particular against *S. aureus* (three strains), *B. subtilis* and *B. cereus* (Herken et al., 2012) when compared with the effectiveness of standard drugs such as tetracycline and streptomycin. In the study of Bukvički et al. (2016) on EOs of *M. thymifolia* (Scop.) Fritsch, the lowest MIC values (0.0312 mg/mL) were reported for three bacteria, viz. *B. cereus*, *L. monocytogenes* and *S. enteritidis*. For *E. coli*, the MIC value was twice more (0.062 mg/mL) and the lowest antibacterial property was achieved for *P. aeruginosa* and *P. fulva* LV1, with MIC values of 0.25 mg/mL and 0.5 mg/mL, respectively. The low to negligible activity observed for the EO from *M. thymifolia* may be explained with the presence of low levels of antimicrobial components such as thymol accounting for only 0.5% of the total composition.

2.4.3. Antifungal activities

Some species of the genus *Micromeria* showed various levels of antifungal potentials. Marinković et al. (2002) reported strong antifungal activity of EOs of *M. thymifolia* (Scop.) Fritsch, *M. albanica* (Griseb. ex K. Maly) Silic and *M. dalmatica* Benth. against seven phytopatogenic fungal strains, namely *A. niger*, *A. ochraceus*, *C. cladosporioides*, *P. ochrochloron*, *P. helianthi*, *T. viride* and *F. tricinctum* (Table 5). The oil of *M. thymifolia* (Scop.) Fritsch showed an MIC value of 0.4 µL/mL against *P. ochrochloron*, while for the rest of fungal strains, the obtained MIC value was 2.0 µL/mL. The positive control, the antifungal drug bifonazole showed an MIC value between 2.0 and 4.0 µL/mL, as well. The oil of *M. albanica* (Griseb. ex K. Maly) Silic was shown to be active against *P. helianthi* (MIC = 0.2 µL/mL) as well as other tested fungal strains (MIC = 0.4 µL/mL). As being reported, the antifungal MIC values of *M. dalmatica* Benth. EO were 0.4 µL/mL against *T. viride* and *F. tricinctum* and 0.2 µL/mL against *A. niger*, *A. ochraceus*, *C. cladosporioides*, *P. ochrochloron* and *P. helianthi*. The EO of *M. albanica* and *M. dalmatica* Benth. exhibited the highest potency, while the least antifungal activity was due to *M. thymifolia* (Scop.) Fritsch EO. In a related study dealing with the antifungal assessments against *C. albicans*, hydrodistilled EO, steam-distilled EO and pulegone, each at a concentration of 10-25 µL/disc of *M. cilicica* Hausskn. ex P.H.Davis, showed inhibition zone diameters (IZDs) of 28-34, 13-21 and 31-44 mm, respectively. In addition, IZD of the *n*-hexane extract of this plant (18-26 mm) was higher than its chloroform extract (15-19 mm), while the ethyl acetate extract was inactive at tested concentrations (Duru et al., 2004). The effect of the EO component pulegone and of the water extract observed on *C. albicans* was found to be approximately twice more than that of nystatin (100 U), the reference drug. Similar results were obtained against *C. albicans* also with the EO distilled from the aerial parts of *M. cristata* subsp. *phrygia* (Tabanca et al., 2001) using ketoconazole as standard drug and positive control. Güllüce et al. (2004) reported that the EO of *M. fruticosa* subsp *serpyllifolia* [now considered a synonym of *Clinopodium serpyllifolium* (M.Bieb.) Kuntze] displayed low level of antifungal properties with IZDs of 17, 21, 14 and 21 mm for *C. albicans*, *A. flavus*, *Rhizopus* spp and *S. minor*, respectively (Table 6). This study revealed that the EO of *M. fruticosa* subsp *serpyllifolia* was not at all active against *A. alternata*, *A. versicolor*, *F. acuminatum*, *F. oxysporum*, *F. solani*, *F. tabacinum*, *M. fructicola*, *Penicillium sp pl*, *R. solani*, *S. sclerotiorum*, *T. mentagrophytes* and *T. rubrum*. Amphotericin B was used as a standard antifungal drug and positive control. El-Seedi et al. (2008) evaluated the antifungal behavior of *M. nubigena* H.B.K. EO, its distillate obtained after treatment with β-glucosidase of the aqueous residue (OBGF), and thymol, as the main constituent of the oil, against *C. albicans*, *B. cinerea* and *A. niger*. Although the EO showed IZDs of 14.5, 11 and 13.5 mm against these fungi, the OBGF was found to be inactive and the highest IZD values were obtained with thymol, with values of 21.5. 20.5 and 14 mm, respectively. Moreover, mediocre antifungal activities were reported for EO of *M. fruticosa* (L.) Druce subsp. *brachycalyx* P.H. Davis against *S. cerevisiae* and *K. fragilis* (Toroglu, 2011) as well as EO of *M. inodora* (Desf.) Benth. versus strains of *C. albicans* ATCC 10231 and *C. albicans* IP 444 (Benomari et al., 2016). Furthermore, the minimum fungicidal concentration (MFC) and the best antifungal activity for the EO of *M. thymifolia* (Scop.) Fritsch was

Table 4
Antibacterial activities of the extracts and essential oils of some species of *Micromeria* genus worldwide.

Sample		*Micromeria* species	Extracting solvent(s)	IZD (mm) [a]	MIC [b] value	MBC [c] value	Bacterial strain	Ref.
EO [d]		*M. thymifolia* (Scop.) Fritsch	-	15-21 [e]	NR [g]	NR	*S. aureus*	(Marinković et al., 2002)
				NA [f]			*P. aeruginosa*	
				14-15 [e]			*E. coli*	
				20-26 [e]			*B. subtilis*	
				NA-14 [e]			*S. faecalis*	
				26-36 [e]			*M. luteus*	
		M. albanica (Griseb. ex K. Maly) Silic		NA-18 [e]			*S. aureus*	
				NA-12 [e]			*P. aeruginosa*	
				12-15 [e]			*E. coli*	
				NA-25 [e]			*B. subtilis*	
				NA-14 [e]			*S. faecalis*	
				22-30 [e]			*M. luteus*	
		M. dalmatica Benth.		NA-15 [e]			*S. aureus*	
				NA-12 [e]			*P. aeruginosa*	
				12-14 [e]			*E. coli*	
				18-25 [e]			*B. subtilis*	
				NA-12 [e]			*S. faecalis*	
				12-21 [e]			*M. luteus*	
EO	HD [h]	*M. cilicica* Hausskn. ex P.H.Davis	-	9-20 [j]	NR	NR	*S. aureus*	(Duru et al., 2004)
				10-19 [j]			*M. luteus*	
				9-15 [j]			*E. aerogenes*	
				NA-17 [j]			*S. typhimurium*	
				12-21 [j]			*B. subtilis*	
				12-17 [j]			*B. cereus*	
				12-13 [j]			*E. coli*	
				9-13 [j]			*P. aeruginosa*	
				11-19 [j]			*S. mutans*	
	SD [i]			11-23 [j]			*S. aureus*	
				10-16 j			*M. luteus*	
				14-22 [j]			*E. aerogenes*	
				14-15 [j]			*S. typhimurium*	
				11-16 [j]			*B.subtilis*	
				13-17 [j]			*B. cereus*	
				NA			*E. coli*	
				9-15 [j]			*P. aeruginosa*	
				NA			*S. mutans*	
	Pulegone			17-22 [j]			*S. aureus*	
				11-18 [j]			*M. luteus*	
				11-13 [j]			*E. aerogenes*	
				22-23 [j]			*S. typhimurium*	
				11-14 [j]			*B. subtilis*	
				14-17 [j]			B. cereus	
				8-11 [j]			E. coli	
				9-10 [j]			P. aeruginosa	
				10-15 [j]			S. mutans	

Table 4 Continued

Sample	*Micromeria* species	Extracting solvent(s)	IZD (mm) [a]	MIC [b] value	MBC [c] value	Bacterial strain	Ref.
Extract	*M. cilicica* Hausskn. ex P.H.Davis	Hexane	NA-15 [j]	NR	NR	*S. aureus*	(Duru et al., 2004)
			13-16 [j]			*M. luteus*	
			10-15 [j]			*E. aerogenes*	
			10-14 [j]			*S. typhimurium*	
			9-16 [j]			*B. subtilis*	
			10-12 [j]			*B. cereus*	
			10-16 [j]			*E. coli*	
			10-17 [j]			*P. aeruginosa*	
			NA			*S. mutans*	
		Chloroform	12-14 [j]			*S. aureus*	
			NA-10 [j]			*M. luteus*	
			NA-8 [j]			*E. aerogenes*	
			8-11 [j]			*S. typhimurium*	
			11-13 [j]			*B. subtilis*	
			8-11 [j]			*B. cereus*	
			NA-9 [j]			*E. coli*	
			NA-8 [j]			*P. aeruginosa*	
			NA			*S. mutans*	
		Ethyl acetate	9-11 [j]			*S. aureus*	
			8-11 [j]			*M. luteus*	
			8-11 [j]			*E. aerogenes*	
			9-11 [j]			*S. typhimurium*	
			8-12 [j]			*B. subtilis*	
			9-11 [j]			*B. cereus*	
			8-10 [j]			*E. coli*	
			8-12 [j]			*P. aeruginosa*	
			8-12 [j]			*S. mutans*	
EO	*M. fruticosa* subsp *serpyllifolia* [k]	-	NA	NR	NR	*A. baumanii*	(Güllüce et al., 2004)
			15			*B. macerans*	
			14			*B. megaterium*	
			10			*B. subtilis A57*	
			14			*B. subtilis A77*	
			6			*B. abortus*	
			NA			*B. cepacia*	
			NA			*C. michiganense*	
			8			*E. cloacae*	
			NA			*E. faecalis*	
			18			*E. coli*	
			12			*K. pneumoniae*	
			NA			*P. vulgaris A161*	
			12			*P. vulgaris Kukem-1329*	
			NA			*P. aeruginosa ATCC-9027*	
			9			*P. aeruginosa ATCC-27859*	
			12			*P. syringae*	
			16			*S. enteritidis*	

Table 4 Continued

Sample	*Micromeria* species		Extracting solvent(s)	IZD (mm) [a]	MIC [b] value	MBC [c] value	Bacterial strain	Ref.
EO	*M. fruticosa* subsp *serpyllifolia* [k]		-	11	NR	NR	*S. aureus* A215	(Güllüce et al., 2004)
				NA			*S. aureus* ATCC-29213	
				NA			*S. epidermis*	
				10			*S. pyogenes* ATCC-176	
				NA			*S. pyogenes* Kukem-676	
				NA			*X. campestris*	
EO	Oil	*M. nubigena* H.B.K. [m]	-	7.5	128 µg/mL	NR	*S. aureus*	(El-Seedi et al., 2008)
				8	64 µg/mL		*K. pneumonia*	
				7.5	64 µg/mL		*E. coli*	
				6	1024 µg/mL		*P. aeruginosa*	
	OBGF [l]			0	NR		*S. aureus*	
				0	NR		*K. pneumonia*	
				0	NR		*E. coli*	
				0	NR		*P. aeruginosa*	
	Thymol			16.5	32 µg/mL		*S. aureus*	
				23.5	16 µg/mL		*K. pneumonia*	
				24	32 µg/mL		*E. coli*	
				18.5	16 µg/mL		*P. aeruginosa*	
Extract		*M. cilicica* Hausskn. ex P.H.Davis	Methanol [n]	8.7-13.6	40 mg/m	NR	S. aureus	(Dulger, 2008)
				10.4-15.8	25 mg/mL		*S. sanguis*	
				8.1-11.0	25 mg/mL		*E. coli*	
				9.6-13.4	40 mg/mL		*P. aeruginosa*	
				10.2-15.6	40 mg/mL		*K. pneumoniae*	
		M. dolichodontha P.H. Davis		NA-12.2	40 mg/mL		*S. aureus*	
				NA-11.8	40 mg/mL		*S. sanguis*	
				NA-10	40 mg/mL		*E. coli*	
				8.2-11.0	40 mg/mL		*P. aeruginosa*	
				NA-10.6	40 mg/mL		*K. pneumoniae*	
		M. cremnophila subsp. *amana*		9.2-15.8	10 mg/mL		*S. aureus*	
				10.2-15.6	10 mg/mL		*S. sanguis*	
				11.2-16.7	25 mg/mL		*E. coli*	
				8.8-16.2	10 mg/mL		*P. aeruginosa*	
				9.6-16.6	10 mg/mL		*K. pneumoniae*	
		M. cilicica Hausskn. ex P.H.Davis	Chloroform	9.2-14.6	25 mg/mL		*S. aureus*	
				10.8-18.8	10 mg/mL		*S. sanguis*	
				10.6-16.2	10 mg/mL		*E. coli*	
				8.4-11.8	40 mg/mL		*P. aeruginosa*	
				10.0-14.6	25 mg/mL		*K. pneumoniae*	
		M. dolich odontha P.H. Davis		NA-12.6	40 mg/mL		*S. aureus*	
				NA-12.8	40 mg/mL		*S. sanguis*	
				NA-12.0	40 mg/mL		*E. coli*	
				8.8-13.8	25 mg/mL		*P. aeruginosa*	
				8.4-12.8	40 mg/mL		*K. pneumoniae*	

Table 4 Continued

Sample	*Micromeria* species	Extracting solvent(s)	IZD (mm) [a]	MIC [b] value	MBC [c] value	Bacterial strain	Ref.
Extract	*M. cremnophila* subsp. *amana*	Chloroform	10.8-17.2	1.0 mg/mL	NR	*S. aureus*	(Dulger, 2008)
			9.8-17.8	1.0 mg/mL		*S. sanguis*	
			10.4-16.8	40 mg/mL		*E. coli*	
			11.8-18.4	1.0 mg/mL		*P. aeruginosa*	
			10.2-17.0	1.0 mg/mL		*K. pneumoniae*	
EO	*M. fruticosa* (L.) Druce subsp *brachycalyx* P.H. Davis	-	8 °	NR	NR	*E. coli*	(Toroglu, 2011)
			10 °			*M. luteus*	
			7 °			*S. aureus*	
			8 °			*M. smegmatis*	
			14 °			*P. pyocyaneus*	
			8 °			*Y. enterolitica*	
			8 °			*A. hydrophila*	
			7 °			*E. faecalis*	
			8 °			*B. megaterium*	
			10 °			*S. faecalis*	
			8 °			*B. brevis*	
EO	*M. congesta* Boiss. & Hausskn. ex Boiss.	-	9-15 [p]	NR	NR	*M. luteus*	(Herken et al., 2012)
			26-31 [p]			*S. aureus*	
			25-30 [p]			*S. aureus* ATCC 25923	
			24-27 [p]			*S. aureus* ATCC 25933	
			16-20 [p]			*E. coli 0157:H7*	
			17-21 [p]			*E. coli* ATCC 25922	
			25-35 [p]			*B. subtilis*	
			18-23 [p]			*B. cereus*	
			6-10 [p]			*E. faecalis*	
			11-16 [p]			*Y. enterocolitica*	
			8-11 [p]			*P. aeruginosa*	
EO	*M. barbata* Fisch. & C.A.Mey. (syn. of M. douglasii Benth)	-	10-11	NR	NR	*E. coli*	(Alwan et al., 2016)
			18			*S. aureus*	
			13			*Salmonella* spp.	
			18			*Listeria innocua*	
			18			*Listeria innocua*	
			12			*E. faecalis*	
			30			*C. albicans*	
EO	*M. inodora* (Desf.) Benth.	-	19	500 µg/mL	NR	*B. cereus*	(Benomari et al., 2016)
			17	500 µg/mL		*B. subtilis*	
			23	60 µg/mL		*S. aureus* ATCC 25923	
			21	60 µg/mL		*S. aureus* ATCC 33862	
			22	60 µg/mL		*S. aureus* ATCC 25923	

Table 4 Continued

Sample	*Micromeria* species	Extracting solvent(s)	IZD (mm) [a]	MIC [b] value	MBC [c] value	Bacterial strain	Ref.
EO	*M. inodora* (Desf.) Benth.	-	14	500 µg/mL	NR	*E. faecalis*	(Benomari et al., 2016)
			8	4000 µg/mL		*L. monocytogenes*	
			6	ND		*P. aeruginosa*	
			6	ND		*P. fluorescens*	
			7	ND		*S. enteritidis*	
			7	4000 µg/mL		*E. coli*	
			8	4000 µg/mL		*K. pneumoniae*	
EO	*M. thymifolia* (Scop.) Fritsch	-	NR	0.0312 mg/mL	NR	*B. cereus*	(Bukvički et al., 2016)
				0.062 mg/mL		*E. coli*	
				0.0312 mg/mL		*L. monocytogenes*	
				0.0312 mg/mL		*S. enteritidis*	
				0.25 mg/mL		*P. aeruginosa*	
				0.5 mg/mL		*P. fulva* LV1	
Extract	*M. graeca* (L.) Benth. ex Rchb.	Hexane-Ethanol	NR	> 2000 µg/mL	> 2000 µg/mL	*S. aureus* ATCC 6538	(Brahmi et al., 2017)
				> 2000 µg/mL	> 2000 µg/mL	*S. aureus C* 100459	
				> 2000 µg/mL	> 2000 µg/mL	*P. aeruginosa*	
				> 2000 µg/mL	> 2000 µg/mL	*E. coli*	
EO	*M. barbata* Fisch. & C.A.Mey. (syn. of M. douglasii Benth)	NR	NR	1/1000	NR	*M. kansasii* (ATCC 12478)	(El Omari et al., 2019)
				1/500		*M. gordonae* (ATCC 14470)	
				1/1000		*M. tuberculosis* (ATCC 27294)	
				1/250 [q]		*M. tuberculosis* MDR (CMUL 157)	

[a] IZD: inhibition zone diameter; [b] MIC: Minimum inhibitory concentration; [c] MBC: Minimum bactericidal concentration; [d] EO: Essential oil; [e] Over the essential oil concentration range 1-10 µL; [f] NA: Not active; [g] NR: Not reported; [h] HD: Hydrodistillation; [i] SD: Steam distillation; [j] Over the essential oil concentration range of 10-25 µL/disc; [k] Plant methanol extract was found to be insensitive against all the bacterial strains; [l] OBGF: β-Glucosidase fraction; [m] Plant EtOH extracts were found to be insensitive against all the bacterial strains; [n] Over the methanol extract concentration range of 10-1000 µg/disk; [o] For 2 µLof the essential oil; [p] Over the essential oil concentration range 30-50 µL; [q] the results represent the higher essential oils dilution conferring a complete growth inhibition of the tested strain.

Table 5
Antifungal activities of the extracts and essential oils of some species of *Micromeria* genus.

Sample		*Micromeria* species	Extracting solvent(s)	Fungi	Antifungal activity			Ref.
					MIC [a]	MBC [b]/ MFC [c]	IZD [d] (mm)	
EO		*M. thymifolia* (Scop.) Fritsch	-	*A. niger*	2.0 µL/mL	NR [f]	NR	(Marinković et al., 2002)
				A. ochraceus	2.0 µL/mL			
				C. cladosporioides	2.0 µL/mL			
				P. ochrochloron	0.4 µL/mL			
				P. helianthi	2.0 µL/mL			
				T. viride	2.0 µL/mL			
				F. tricinctum	2.0 µL/mL			
		M. albanica (Griseb. ex K. Maly) Silic		*A. niger*	0.4 µL/mL			
				A. ochraceus	0.4 µL/mL			
				C. cladosporioides	0.4 µL/mL			
				P. ochrochloron	0.4 µL/mL			
				P. helianthi	0.2 µL/mL			
				T. viride	0.4 µL/mL			
				F. tricinctum	0.4 µL/mL			
		M. dalmatica Benth.		*A. niger*	0.2 µL/mL			
				A. ochraceus	0.2 µL/mL			
				C. cladosporioides	0.2 µL/mL			
				P. ochrochloron	0.2 µL/mL			
				P. helianthi	0.2 µL/mL			
				T. viride	0.4 µL/mL			
				F. tricinctum	0.4 µL/mL			
EO	HD [g]	*M. cilicica* Hausskn. ex P.H.Davis	-	*C. albicans*	NR	NR	28-34	(Duru et al., 2004)
	SD [h]						13-21	
	Pulegone						31-44	
Extract			Hexane				18-26	
			Chloroform				15-19	
			Ethyl acetate				NA	

Table 5 Continued

Sample		*Micromeria* species	Extracting solvent(s)	Fungi	Antifungal activity			Ref.
					MIC [a]	MBC [b]/ MFC [c]	IZD [d] (mm)	
EO		*M. fruticosa subsp serpyllifolia* [i]	-	*C. albicans*	NR	NR	17	(Güllüce et al., 2004)
				A. alternata			NA	
				A. flavus			21	
				A. varsicolor			NA	
				F. acuminatum			NA	
				F. oxysporum			NA	
				F. solani			NA	
				F. tabacinum			NA	
				M. fructicola			NA	
				Penicillium spp			NA	
				Rhizopus spp			14	
				R. solani			NA	
				S. sclerotiorum			NA	
				S. minor			21	
				T. mentagrophytes			NA	
				T. rubrum			NA	
EO	Oil	*M. nubigena* H.B.K.	-	*C. albicans*	NR	NR	14.5	(El-Seedi et al., 2008)
				B. cinerea			11	
				A. niger			13.5	
	OBGF [j]			*C. albicans*			NA	
				B. cinerea			NA	
				A. niger			NA	
	Thymol			*C. albicans*			21.5	
				B. cinerea			20.5	
				A. niger			14	
EO		*M. fruticosa* (L.) Druce subsp. *brachycalyx* P.H. Davis	-	*S. cerevisiae* [l]	NR	NR	10	(Toroglu, 2011)
				K. fragilis [l]			16	
EO		*M. inodora* (Desf.) Benth.	-	*C. albicans* ATCC 10231	1000 µg/mL	NR	11	(Benomari et al., 2016)
				C. albicans IP 444	1000 µg/mL		13	
EO		*M. thymifolia* (Scop.) Fritsch	-	*C. humilis* LVL 1	> 0.5 mg/mL	NA	NR	(Bukvički et al., 2016)
				C. krusei LVL 12	0.25 mg/mL	0.5 mg/mL		
				G. klebanhii LVL 3	0.0625 mg/mL	NA		
				P. anomala OC 70	0.25 mg/mL	0.5 mg/mL		
				P. anomala OC 71	0.125 mg/mL	0.25 mg/mL		
				P. membranaefaciens CBS 5759	0.25 mg/mL	0.5 mg/mL		
				P. membranaefaciens DBVPG 3003	0.25 mg/mL	0.5 mg/mL		

[a] MIC: Minimal inhibitory concentration; [b] MBC: Minimum bactericidal concentration; [c] MFC: Minimum fungicidal concentration; [d] IZD: inhibition zone diameter (mm); [e] EO: Essential oil; [f] NR: Not reported; [g] HD: Hydrodistillation; [h] SD: Steam distillation; [i] Plant methanol extract was found to be insensitive against all the fungal strains; [j] β-Glucosidase fraction; [k] Plant EtOH extracts were found to be insensitive against all the fungal strains; [l] Using 2 µL of the essential oil.

noted against *P. anomala* OC71 (0.25 mg/mL) and the same for *C. krusei* LVL12, *P. anomala* OC70, *P. membranaefaciens* CBS 5759 and *P. membranaefaciens* DBVPG 3003 (0.5 mg/mL). However, the oil showed no activity vs. *C. humilis* LVL 1 and *G. klebanhii* LVL 3.

2.4.4. Enzyme inhibitions

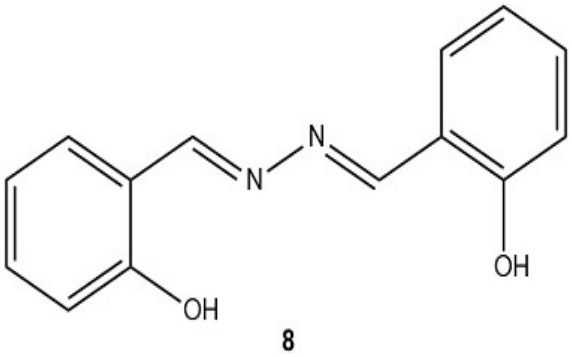
2.4.4.1. Anticholinesterase activity

Plants are rich sources of compounds which may interact with the acetylcholinesterase system. Fisostigmin isolated from *Physostigma venenosum* Balf. and pilocarpin obtained from *Pilocarpus jaborandi* Holmes are among the most known ones and currently used in ophthalmology (Goodman, 1996). Several compounds, mainly alkaloids, with anticholinesterase action have been isolated from plant species and their relevance in several diseases such as Alzheimer's and Parkinson's diseases (Duvoisin, 1967; Lang and Blair, 1989; Giacobini, 1990; Konishi et al., 2015) is in the limelight together with their potential as naturally occurring insecticides (Benamar et al., 2016; Benamar et al., 2017). The search of new active agonists and antagonists of the acetylcholinesterase is nowadays the main target of several researchers, and in the present section we report the results obtained from *Micromeria* spp. Öztürk et al. (2009) have evaluated the anticholinesterase activity of the organic extracts of *M. juliana* (L.) Bentham ex Reichb. including light petroleum, acetone and methanol ones. As shown, using 200 µg portions of each extract, anticholinesterase activities were found to be, respectively, -5.9 ± 4.1 µg/mL, 35.3 ± 3.1 µg/mL and -7.6 ± 6.8 µg/mL, using galantamine as a positive control (74.0 ± 0.8, IC_{50}: 5.0 ± 0.1 µg/mL). In addition, the reported IC_{50} values were higher than 200 µg/mL for all the employed organic solvents. Furthermore, using the butyryl-cholinesterase (BChE) assay on 200 µg of the organic extracts, the activities were found to be respectively 40.9 ± 3.1 µg/mL, 52.4 ± 1.8 µg/mL and -6.2 ± 2.3 µg/mL, comapared to galantamine used as positive control (75.0 ± 0.6 µg/mL, IC_{50}: 50.8 ± 0.9 µg/mL). In this relation, IC_{50} values of the light petroleum and methanol extracts were higher than 200 µg/mL, while the IC_{50} of the acetone extract was 185.6 ± 1.9 µg/mL. The composition of the most active extract was tentatively determined by GC-MS after fractionation on silica gel and eicosene, cembrene, thymoquinone, phytone were among the main components even if several of the components remained unidentified. The characterized compounds in the report of Öztürk et al. (2011) were also tested for their anticholinesterase and antioxidant potentialities, together with the crude organic extracts. From the results obtained, three of the isolated compounds exhibited a medium-high acetylcholinesterase inhibitory activity, while the other compounds were found to be inactive. In particular, sudachitin, isomucronulatol and ursolic acid showed high activity, with values comparable with those of galantamine as a standard acetylcholinesterase inhibitor drug. These values were, respectively for the acetyl- and butyryl-cholinesterase and at a concentration of 200 µM, 65.2 ± 0.82 µM and 78.3 ± 1.70 µM (IC_{50}: 140 ± 0.88 µM and 60.1 ± 0.66 µM) for sudachin, 75.2 ± 0.78 µM and 81.3 ± 1.33 µM (IC_{50}: 118 ± 1.90 µM and 56.2 ± 0.45 µM) for isomucronulatol and 54.3 ± 0.21 µM and 78.8 ± 0.62 µM (IC_{50}: 93.8 ± 1.00 µM and 41.1 ± 0.78 µM) for ursolic acid. However, at different concentrations, galantamine showed similar results on the inhibition of both cholinesterases with values ranging from 74.0 ± 0.81 µM to 75.0 ± 0.60 µM (IC_{50}: 5.01 ± 0.11 µM and 50.9 ± 0.95 µM). These data clearly indicate that isomucronulatol may have an inhibitory activity on acetyl-cholinesterase comparable with those of galantamine but at higher concentrations (>20- fold higher), while the other two components resulted to be less effective in inhibiting the same enzyme. In the case of the butyryl-cholinesterase, all the compounds exerted an activity comparable with those observed for the standard drug used as positive control. The resulted extracts were found to be less active than the purified components, whereas the acetone extract showed the best result, even if the observed values may suggest that no synergistic action among the constituents may occur (Öztürk et al., 2011). A modest anti-cholinesterase activity was also observed in the chloroform and methanol extracts (500 µg/mL) from *M. fruticosa* subsp. *brachycalyx* P.H.Davis (syn. of *Clinopodium serpyllifolium* subsp. *brachycalyx* (P.H.Davis) Bräuchler) 39.50 ± 0.63% and 35.85 ± 2.89%, respectively, when compared with standard galantamine (93.14 ± 0.14%) (Taskin et al., 2020). All these papers report a modest effectiveness in anticholinesterase tests but provide the basis for further studies in this field. In fact, this receptor is involved in several neurologic diseases such as Alzheimer's and Parkinson's diseases (Duvoisin, 1967; Lang and Blair, 1989; Giacobini, 1990; Konishi et al., 2015).

2.4.4.2. Tyrosinase inhibition

Tyrosinase has been recognized as an enzyme being involved in the key reactions during the biosynthesis of melanins (Hong and Yang, 2013; Kim et al., 2016). It has been shown that the inhibition of tyrosinase is one of the most effective ways to overcome a variety of skin disorders and to inhibit the browning processes of plant-derived foods (Ullah et al., 2016). Therefore, the inhibitors of this enzymatic system are important active ingredients not only in the cosmetic and medicinal fields, but also are relevant as natural additives in the food industry. Brahmi et al. (2017) have determined the inhibition potential of tyrosinase using the L-DOPA (L-3,4-dihydroxyphenylalanine) assay. Accordingly, the ethanol extract of *M. graeca* (L.) Benth. ex Rchb., was not so effective as an inhibitor (IC_{50}: 302 ± 62 µg/mL) of anti-tyrosinase activity when compared to that of kojic acid, a reference inhibitor, which showed an IC_{50} value of 8.9 µg/mL. The literature search showed only this one study regarding to the tyrosinase inhibitory relevance of *M. graeca* extract with modest results. Starting from this basis, it would be advisable to explore also other species of the genus for the possible presence of more

efferctive phytoconstituents responsible for this activity. Salicylalazine (Fig. 3) was recently isolated from the choloroform extract of *M. biflora* (Buch.-Ham. ex D.Don) Benth. (Rauf et al., 2021) and resulted to be more effective than kojic acid in inhibiting mushroom tyrosinase (89.4% inhibition vs 86.3%, respectively) with an IC_{50} value of 21.4 ± 2.43 µM, while the standard kojic acid showed an IC_{50} value of 47.6 ± 0.67 µM.



8

Fig. 3. Molecular structure of salicylalazine.

Docking studies performed on tyrosinase showed interactions with the subunit of enzyme containing the two Cu atoms coordinated with six histidine residues. Salicylalazine forms coordination bonds with both Cu atoms via the oxygen atoms of hydroxyl substituents. Furthermore, the two phenyl rings form π-π stacking interactions with two histidine residues present in this enzyme region (His244 and His263), while kojic acid interacts with only one histidine residue (His263) and presents the same kind of interaction. The observed binding energy values for salicylalazine and kojic acid were -6.7148 kcal/mol and -5.3222 kcal/mol, respectively, thus confirming the high affinity of salicylalazine toward this target enzyme.

2.4.4.3. Urease inhibition

In the same work by Rauf et al. (2021), salicylalazine was also tested for the antiurease activity and exhibited 88.7% inhibition (IC_{50} = 12.4 ± 1.10 µM) when compared with the standard thiourea (98.4% inhibition, IC_{50} = 21.0 ± 0.21 µM). Docking simulations showed that salicylalazine binds away from the bi-nickel center and interacts with the flap residues Arg439 and His593. It was also shown that the phenyl group interacts by π-π stacking with two histidine residues (His492 and His519) present in the binding site and the hydroxyl group forms a hydrogen bond with Gly550. The result of this interaction is a reduced mobility of the active site flap and also in this case the binding energy of -5.9618 kcal/mol confirmed the high affinity for the active site. Urease inhibition was also observed but in minor extent in the methanol and chloroform extracts obtained from *M. fruticosa* subsp. *brachycalyx* P.H.Davis (syn. of *Clinopodium serpyllifolium* subsp. *brachycalyx* (P.H.Davis) Bräuchler) (Taskin et al., 2020). In particular, the methanol extract (11.39 ± 1.98%) was found to be more active than the chloroform one (6.57 ± 1.73%) when tested at the concentration of 12.5 µg/mL and the observed difference is most possibly due to the higher content of flavonoid and phenol contents in the former extract. However, the activity was lower when compared with the used standard thiourea (78.54 ± 0.60%).

2.5. Miscellaneous

There are numerous reports in literature dealing with the antidepressant potentialities of flavonoids and several of these have been identified as constituents of plant species traditionally employed as tranquillizers for their potential sedative and antispasmodic properties (Venditti et al., 2014b; Venditti et al., 2015c; Venditti et al., 2017a; Venditti and Bianco, 2018). The common flavone apigenin (4′,5,7-trihydroxyflavone) is well-known for its various health promoting activities (Salehi et al., 2019). Flavonoids have been proved to present a selective affinity with a partial agonistic mechanism toward the benzodiazepine receptors (Medina et al., 1989; Medina et al., 1997) and this gives one further evidence to substantiate their wide use as natural antidepressant agents. The cytotoxic potential of the acetone extract obtained from *M. nervosa* (Desf.) Benth. and the isolated components micromeriol (**6**), nervosane (**7**), β-sitosterol, oleanolic acid and ursolic acid were assessed in the work of Abdelwahab et al. (2015) against several cancer cell lines involving liver (SNU-398, Hep G2), leukemia (CCRF-CEM, HL-60 TB), colon (COLO 205, HCT-116), urinary bladder (HT-1376, UMUC-3), stomach (MKN-28, NCI-N87), ovary (NIH:OVCAR-3, SK-OV-3), and uterus (MES-SA, MES-SA/MX2). As being reported, the crude extract showed interesting ED_{50} (µg/mL) values against Hep G2, COLO 205, MKN-28 and NIH:OVCAR-3 with ED_{50} 9.15 (±0.05), 14.85 (±0.10), 18.20 (±0.12) and 7.87 (±0.05), respectively, while the resulted ED_{50} was more than 50 and even 100 µg/mL against the other cell lines. Among the isolates, micromeriol (**6**) resulted to be the most effective compound and exerted interesting activities toward SNU-398, Hep G2, COLO 205 and MKN-28 with ED_{50} values of 15.10 (±0.10), 5.18 (±0.05), 10.05 (±0.05) and 13.65 (±0.08) µg/mL, respectively. These are obviously promising results, but further studies are still necessary to validate these data also in *in vivo* models. The antiaflatoxinogenic activity in *Aspergillus flavus* was observed for an aqueous extract obtained from *M. graeca* by El Khoury et al. (2017). The authors reported that the extract almost completely inhibits aflatoxin production (99.2%) at a concentration of 10 mg/mL through an interaction at the transcriptomic level and without reducing fungal growth. Similar results have recently been observed also in *Linaria purpurea* (Frezza et al., 2019b) and may represent interesting impacts since low toxicity natural products could be applied in the food industry as green methods for the control of aflatoxins instead of synthetic derivatives. Unfortunately, the authors did not characterize the aqueous extract and therefore it is not possible to verify that similarily to what observed in *L. purpurea*,

also in the case of *M. graeca* the bioactivity is due to the presence of some iridoids in the extract.

3. Concluding remarks

An overview of the literature on different *Micromeria* species reveals the presence of novel natural compounds (**1**-**7**) whose structures are shown in Fig. 1. Moreover, most of the species of *Micromeria* are potential sources of EOs particularly rich in oxygenated monoterpenes. Many papers demonstrated the antioxidant, antibacterial, antifungal, anticholinesterase activity, tyrosinase inhibition and antinociceptive activity of *Micromeria* species, indicating the importance of this genus in a variety of medical disciplines. In this context, it should be noted that a large number of species of this genus have been scarcely studied. Therefore, it is auspicable that further studies will be conducted on the unreported species for both the bioactivity and the phytochemical compositions. Finally, from the chemotaxonomical standpoint, the widespread presence of rosmarinic acid as a marker compound in several entities of the genus *Micromeria* could be underlined and it is advisable that further studies may help to shed light on the question of the presence of iridoids, a class of natural compounds that has a particular importance as chemotaxonomic marker in the whole Lamiaceae family.

Microorganisms abbreviations

Acinetobacter baumanii: *A. baumanii*; *Alternaria alternata*: *A. alternata*; *Aspergillus flavus*: *A. flavus*; *Aspergillus niger*: *A. niger*; *Aspergillus ochraceus*: *A. ochraceus*; *Aspergillus versicolor*: *A. versicolor*; *Bacillus cereus*: *B. cereus*; *Bacillus macerans*: *B. macerans*; *Bacillus megaterium*: *B. megaterium*; *Bacillus subtilis*: *B. subtilis*; *Botrytis cinerea*: *B. cinerea*; *Brucella abortus*: *B. abortus*; *Burkholderia cepacia complex: B. cepacia*; *Candida albicans*: *C. albicans*; *Candida humilis*: *C. humilis*; *Candida krusei*: *C. krusei*; *Cladosporium cladosporioides*: *C. cladosporioides*; *Clavibacter michiganensis*: *C. michiganense*; *Enterobacter aerogenes*: *E. aerogenes*; *Enterobacter cloacae*: *E. cloacae*; *Enterococcus faecalis*: *E. faecalis*; *Escherichia coli*: *E. coli*; *Fusarium tricinctum*: *F. tricinctum*; *Fusarium oxysporum*: *F. oxysporum*; *Fusarium solani*: *F. solani*; *Fusarium tabacinum*: *F. tabacinum*; *Fusarium acuminatum*: *F. acuminatum; Geotrichum klebanhii*: *G. klebanhii*; *Klebsiella pneumoniae*: *K. pneumoniae*; *Kluyveromyces fragilis*: *K. fragilis*; *Micrococcus luteus*: *M. luteus; Monilinia fructicola*: *M. fructicola*; *Penicillium ochrochloron*: *P. ochrochloron*; *Penicillium spp*: *P. spp*; *Phomopsis helianthi*: *P. helianthi*; *Pichia anomala*: *P. anomala*; *Pichia membranaefaciens*: *P. membranaefaciens*; *Proteus vulgaris*: *P. vulgaris*; *Pseudomonas aeruginosa*: *P. aeruginosa*; *Pseudomonas syringae*: *P. syringae*; *Rhizoctonia solani*: *R. solani*; *Rhizopus spp*: *R. spp; Saccharomyces cerevisiae*: *S. cerevisiae*; *Salmonella enteritidis*: *S. enteritidis*; *Salmonella typhimurium*: *S. typhimurium*; *Sclerotinia sclerotiorum*: *S. sclerotiorum*; *Sclorotinia minor*: *S. minor*; *Staphylococcus aureus*: *S. aureus*; *Staphylococcus epidermidis*: *S. epidermidis*; *Streptococcus faecalis*: *S. faecalis*; *Streptococcus mutans*: *S. mutans*; *Streptococcus pyogenes*: *S. pyogenes*; *Streptococcus sanguinis*: *S. sanguinis*; *Trichophyton mentagrophytes*: *T. mentagrophytes*; *Trichophyton rubrum*: *T. rubrum*; *Trichoderma viride*: *T. viride*; *Xanthomonas campestris*: *X. campestris*.

Conflict of interest

The authors declare that there is no conflict of interest.

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