MICROMERIA: CHEMISTRY AND MEDICINAL ACTIVITIES

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The genus *micromeria* is one of the most widespread plant families in the "old world". Its subspecies, especially *Micromeria fruticosa*, have been used by humans for thousands of years. The plant(s), its extracts and its chemical ingredients are reviewed in this article for their reported medicinal/biological activities. In addition, the traditional medicine and ethnobotanical uses are briefly presented.

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Introduction

Plants have been used by human since the very dawn of our kind. They are used as major food source, medicinal-herbal, therapeutic agents, psychoactive and cosmetics. As one of the most common in the "old world",[1] the genus *micromeria* is used by inhabitants of Mediterranean basin for thousands of years, as it is indicated by archeological documentation.[2] Counting the known species, subspecies and varieties of the genus micromeria, the total number may easily reach more than one hundred.[1,3] But in this review we relate only to the subspecies whose chemical compositions have been reported and/or have been published for their biological/medicinal activities.

Special attention is paid to *M. fruticosa* since it is one of the most known species of the genus micromeria and it is one of the most traditionally used as edible and medicinal plant in the middle eastern region. In addition, it is the most investigated and reported of all micromeria subspecies.

The similarity of micromeria subspecies makes it difficult to distinguish them from each other, especially when they grow in the same habitat. But despite this, in traditional Palestinian society, some people, mostly who practiced herbal medicine, could make this distinction: *M. fruticosa* (L.) Druce was used for stomach, intestine pain and inflammation, fever, asthma and respiratory system; while *M. myrtifolia* L. was used to treat skin diseases, heart diseases, digestive system and asthma.[4] On the other hand, ordinary people who use micromeria species for nutrition purposes (mainly as tea flavoring) will not make this distinction.[5] *M. myrtifolia* was also traditionally used to treat digestive system disorders, *M. fruticosa* cured poisoning of some sulfate salts (Cu/Fe/$ZnSO_4$) and in Asia minor and Greece, *M. nervosa* was also commonly used.[6] In recent years, there is a growing interest in cultivation of *M. fruticosa* and the search for optimal conditions that can yield different compositions of the plant, especially the chemical composition of its essential oil.[7] Finally, in traditional Arab medicine, *M. myrtifolia* (infusion) is known as antiseptic and helps in menstrual pain relief.[8]

Medicinal activities of micromeria subspecies (excluding M. fruticosa)

A number of reports are published concerning the medicinal activities of the genus micomeria. A reader-easy-access-summary of these reports is presented in Table 1, followed by a brief discussion on the reported findings. After reviewing Table 1, it is clear that most cited studies obtained the essential oil from the plant species, Some analyzed these oils to find their chemical compositions, but most studies tested the whole oils for medicinal activities. One major reason for this is the growing recognition of the *synergism* between the activities of natural products. This is discussed in the next section. But at the same time, it is important to notice that some major compounds detected in these oils are major sources of the plants activities.

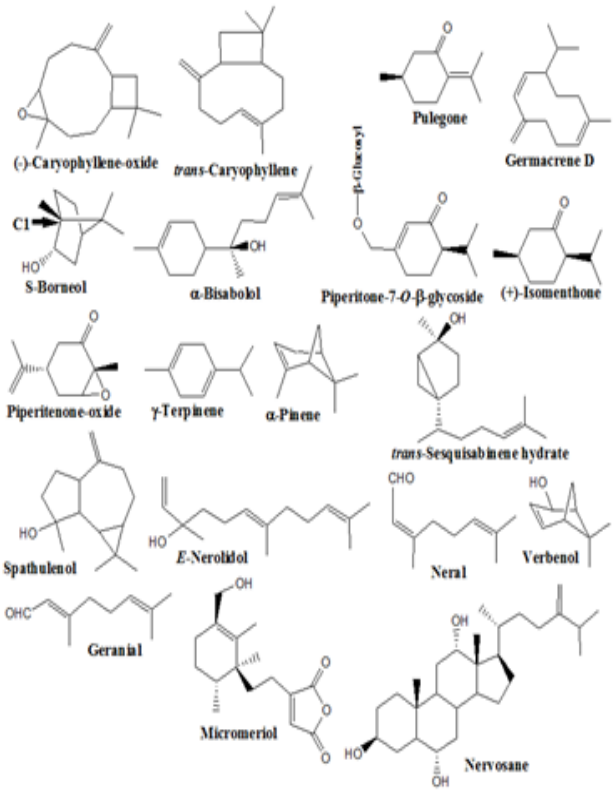

Figure 1. Structures of selected non-phenolic active compounds in *micromeria* ssp.

Table 1. Chemical compositions and medicinal activities of selected micromeria subspecies

Species[A]	Chemical Composition[B]	Medicinal Activities
M. albanica	[9]Essential oil: Piperitenone-oxide (44%), α/β-pinene, limonene, menthone, cuminaldehyde, pulegone, piperitone, piperitone oxide [10]Flavanoids (Thymusin, major)	[11]Antibacterial, antifungal
M. barbata	[12]Ethanolic extract: Chlorogenic acid, Myrcetin, Hespertetin, Quercetin	[12]Antioxidant (ethanolic extract), essential oil activities: [13,14,15]Antimicrobial, [13]antioxidant, [14]sporicidal
M. biflora	[16]Essential oil: *trans*-Caryophyllene (43.7%), (-)-cayrophyllene-oxide, spathulenol, α-humulene, germacrene-D, farnesene, α-myrcene, R(+)-limonene, α-pinene, [17]Essential oil: Caryophyllene-oxide, epi-α-cadinol, β-eudesmol, oplapanone, guaial, *p*-cymene, γ/δ/α-cadinene[C, 18,23,24]Methanol extraction, drying and fractionation with various solvents	Essential oil: [16]Antimicrobial, [19]Antibacterial, [20]Antibacterial (dental) [17]Essential-oil/Ethanolic extract: Anti-inflammatory, anti-arthritis, analgesic, antipyretic, toxic, [18]Antimicrobial: most active was n-hexane fraction, [21]Aqueous/methanolic extract: Antidandruff, [22,24]Methanolic extract: Antioxidant, [23]Antibacterial, antifungal
M. cilicica	[25]Essential oil: Pulegone (65.3%), *cis*/*trans*-*p*-menthone, [26]Acetone extract and its ingredients: Piperitone-7-O-β-D-glucoside, isothymonin-4'-methyl ether,[D] sudachitin, isomucronulatol, rutin, ursolic acid, saccharose	[25]Essential-oil, pure pulegone: antimicrobial, antibacterial, antifungal, [26]Antioxidant, anticholinesterase, [30]Antimicrobial
M. congesta	[27] Piperitenone-oxide (42.5%), pulegone, verbenone	[28]Essential oil: antibacterial, antioxidant
M. cremnophila	[29]Essential oil: Germacrene D (24%), β-caryophyllene, caryophyllene-oxide, *E*-β-farnesene, bicyclogermacrene	[30]Animicrobial
M. cristata	[10](Traces) Luteolin, apigenin, chrysoeriol, diosmetin, acacetin [31]Essential oil: Borneol (32.5%), camphor, caryophyllene-oxide, *trans*-verbenol, [32]Essential oil: Bisabolol (38.5%)[E], verbenol, borneol, caryophyllene-oxide	[31]Antimicrobial (essential oil and pure compounds), See also remark G
M. croatica	[10](Traces) Luteolin, apigenin, chrysoeriol, diosmetin, acacetin, [33]Ethanolic extract: apigenin, luteolin, rosmarinic acid, chlorogenic acid	[33]Ethanolic extract: antioxidant (4 different methods), [34]Methanolic extract: antioxidant, [35]Ethanolic extract: hepatoprotective (CCl_4-induced injury)
M. dalmatica	[10]Flavanoids: (Thymonin, major), [32,36]Pulegone (35.8%), piperitinone, menthone, piperitone	[11]Antibacterial, antifungal, [37]Antibacterial (food)
M. dolichodontha	[38]Essential oil: Isomenthone (23.5%), pulegone, *cis*-piperitone-oxide, piperitone	[30]Antimicrobial
M. fruticulosa	[39]Essential oil: γ -terpinene (14.5%), β-caryophyllene, *p*-cymene, α-pinene β-bisabolene	[39]Antimicrobial
M. graeca	[10](Traces) Luteolin, apigenin, chrysoeriol, diosmetin, acacetin, [40]Essential oil: Caryophyllene-oxide (17.0%), *epi*-α-bisabolol; linalool, β-chamigrene[F], 4[2]Quinic acid (detected by H-NMR)	[41] Antiphytoviral
M. herpyllomorpha	[43]Essential oil: α-Pinene (9.2%), borneol, cubenol, *trans*-Pinocarveol, dehydrosabinene	No reports
M. hyssopifolia	[43]Essential oil: Borneol (13.7%), α-pinene, camphor, *p*-cymene, camphene	
M. inodora	[44]Essential oil: *trans*-sesquisabinene hydrate (20.9 %), *α*-terpinyl acetate, globulol, caryophyllene oxide, *β*-bisabolol	[44]Antimicrobial

M. juliana	[10](Traces) Luteolin, apigenin, chrysoeriol, diosmetin, acacetin, [32]Caryophyllene-oxide (11.2%), caryophellene, germacrene D, spathulenol, [33]Ethanolic extract: apigenin, luteolin, rosmarinic acid, chlorogenic acid, [46]Essential oil: α-Pinene (8.9%), β-pinene, β-caryophyllene, α-gurjunene, linalool, [47]Essential oil: Verbenol (11.8%), thymol, caryophyllene-oxide, borneol, myrtenal[G] , [48]Successive extractions with petroleum ether, ethyl acetate, methanol: Rosmarinic acid, chlorogenic acid, rutin hydrate, caffeic acid, [49]Borneol (9.3%), verbenols, furanoid linalool oxide[H]	[33]Ethanolic extract: antioxidant (4 different methods), [45]Antifungal (methanolic extract), [47,48]Antimicrobial
M. lachnophylla	[43]Essential oil: Borneol (22.0%), bornyl acetate, camphene, camphor, verbenone	Not reported
M. lasiophylla	[43]Essential oil: Borneol (24.9%), linalool, camphor, camphene, α-pinene	Not reported
M. longipedunculata	[51]Essential oil: Spathulenol (33%), piperitone-oxide, piperitone, *p*-cymeme, bicyclogermacrene	Not reported
M. myrtifolia	[52]Essential oil: *trans*-Caryophyllene (15.5%), caryophyllene-oxide, hexadecanoic acid, caryophylla-3,8(13)-dien-5β-ol, germacrene D	[52]Antioxidant [53]Antifungal [54]Cytotoxic
M. nervosa	[55]Carvacrol, [57]Acetone extract, chromatography: Micromeriol, Nervosane,[I] β-sitosterol, oleanolic acid, ursolic acid	[45]Antifungal (methanolic extract), [55]Antimicrobial (various extracts and carvacrol), [56]Antimicrobial (ethanolic extract), [57]Antioxidant, cytotoxic (micromeriol)
M. nubigena	[58]Essential oil: Thymol (36.9%), carvacrol, pulegone, caryophyllene- oxide, *E*-phytol	[58]Antimicrobial (essential oil, thymol, carvacrol)
M. parviflora	[10](Traces) Luteolin, apigenin, chrysoeriol, diosmetin, acacetin [49] Spathulenol (29.9%)	
M. persica	[59]Essential oil: Thymol (33.1%)[J], γ-terpinene, limonene, 1,8-cineole, *p*-cymene	[60]Methanolic extract: antioxidant, antimicrobial
M. pseudocroatica	[10](Traces) Luteolin, apigenin, chrysoeriol, diosmetin, acacetin, [61]Essential oil: Borneol (23.8%), camphor, β-caryophyllene, caryophyllene-oxide, δ-cadinene	Not reported
M. thymifolia	[10]Flavanoids (Thymonin, major), [11]Essential oil: Pulegone (32.8%), piperitenone, piperitone, isomenthone, limonene, [33]Ethanolic extract: apigenin, luteolin, rosmarinic acid, chlorogenic acid	[11]Antibacterial, antifungal, [33]Ethanolic extract: antioxidant (4 different methods), [62]Antimicrobial
M. varia	[43]Essential oil: Borneol (19.2%), α-pinene, *E*-Nerolidol, camphene, camphor, [63]Essential oil: α-Pinene (27.5%), geranial, *trans*-nerolidol, β-caryophyllene-oxide, β-caryophyllene	Not reported

A) Varities and combinations are not presented. B) Selected bioactive compounds. C) In reference 16, *M. biflora* ssp. *arabica* K. Walth was studied, while reference 17 reported the results for *M. biflora* (Buch.-Ham. Ex D. Don) Benth. D) New compounds. E) The major compounds in the essential oils of *M. cristata*,[31,32] are from the same subspecies but from different locations, and authors of reference 32 are aware of that. F) Authors of the article in reference 40 have reported the chemical compositions of *M. graeca* from two different locations, and these compositions are notably different. On the contrary, essential oils of two samples of *M. graeca* from two Croatian islands (Vis, Komiza) show same compositions.[41] G) Even though *M. cristata* and *M. Juliana from* different locations yielded different essential oil compositions (reference 47) compared with previously cited articles, in all cases, antimicrobial activities were indicated. The major compounds found in *M. cristata* essential oil are: Isoborneol (11.3%), borneol, verbenone, 10-*epi*-α-cadinol, thujan-3-ol. H) Differences in essential oils compositions from micromeria subspecies from the same localities were the basis for Kremer *et al*. to determine that the closely related *M. juliana* and *M. kerneri* are different subspecies.[50] Other evidences were also provided. I) New compounds, see Figure 1. J) Concentrations are given before and during flowering season.

The presence of mono-, di- and sesqui-terpenes is notable. Pulegone, piperitenone, piperitenone-oxide, caryophyllene and caryophyllene-oxide(s) are major examples (see Figure 1).

In *M. cristata*, the presence of Borneol and its alcoholic functional group oxidation product, camphor (ketone), is very notable.[31] The natural enantiomeric compositions of each one of these bicyclic compounds totally prefer the C1-S-configuration (C1, indicated in Figure 1), with 100% and 99% respectively. It is worth paying attention to the fact that various locations where these species grow have great influence on the chemical composition of borneol and bisabolol (Figure 1) in *M. cristata*.[31,32] :

Each one of these compounds is widely investigated with or without connection to the genus micromeria, and some of them (piperitenone-oxide, for example) are mentioned in several research articles. However, only medicinal activities connected with micromeria are mentioned. It is interesting to notice that some research workers studied even compounds with low concentrations like the isomeric citrals, geranial and neral (Figure 1).[64] Another interesting group of compounds present in the genus micromeria and widely studied is the group of polyphenolics (Figure 2). For clear polarity and molecular mass properties, polyphenols are not present in the essential oil of the plants, but can be obtained by extraction with polar solvents (water, ethanol, methanol).

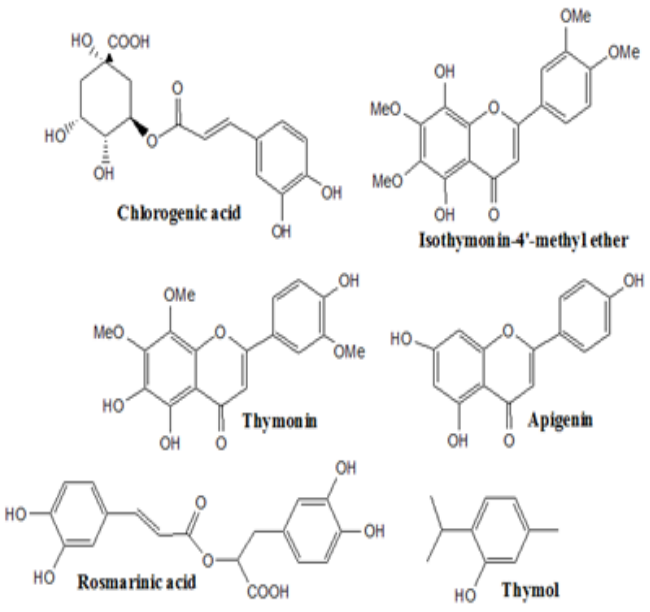

Figure 2. Structures of selected phenolic active compounds in *micromeria* ssp.

Polyphenols are known for their powerful antioxidant capacities, and they are mostly tested for this property and its related activities such as anti-inflammatory and analgesic.

Finally, it is important to point out that there are some papers that have reported chemical compositions and biological activities of micromeria as well as other taxonomic affiliation such as *M. debilis*, known also as *Satureja debilis*. This plant is recently studied and its antimicrobial[65] essential oil has very close composition [β-Pinene (19.3%), geranial, linalool, germacrene, *(E)*-β-caryophyllene; similar to those from other micromeria species. , but despite this, we did not include it in Table 1.

Micromeria fruticosa: from ethnomedicine to up-to-date research

Ethnomedicine

M. fruticosa is the well-known subspecies of the genus micromeria growing on the eastern coast of the Mediterranean, and some its uses are documented in various reports.. It is believed in the Palestinian society that drinking an infusion of *M. fruticosa* leaves and stalks helps in curing different types of paralysis, nervous system disorders and it has calming effect.[66] The use for treating nervous system disorders is mentioned in traditional Palestinian medicine along with other uses: treatments of diabetes, illnesses of respiratory system, especially cough, urinary diseases , headaches and fever.[67]

Sheep and goats that suffer from diarrhoea are made to drink the infused leaves of *M. fruticosa.* [68] This use is similar to one of the uses of this plants for human therapy (see below, section 3).

Chemical composition of *M. fruticosa*

The chemical composition of *M. fruticosa* (and its many subspecies) has been thoroughly studied and published. The first notable fact is that this composition varies extensively according to subspecies and season of harvesting the plant samples. This and five other compounds that have high concentration of *M. fruticosa* are reported in **Table 2.**A careful study of the Table 2 reveals three important facts:

1) Unlike micromeria subspecies, mentioned in Table 1, in *M. fruticosa* essential oils, boneol is not one of the five and Carvacrol) is over 200% and in the fruit ripening season (October-November), compounds can change "ranks" of concentration.

Table 2. Chemical compositions of *M. fruticosa*

Subspecies	Five compounds with highest concentration of essential oils (%)				
[69]*serpyllifolia*	pulegone 33.40	piperitenone 33.10	piperitenone oxide 4.18	spathulenol 3.15	6-allyl-2-cresol 33.07
[70]*giresunica*	pulegone 39.57	menthol 24.27	menthone 24.21	limonene 1.35	germacrene D 1.42
[71]*serpyllifolia*	piperitenone 50.61	pulegone 29.19	isomenthone 3.92	α-pinene 0.79	limonene 0.68
[72]*serpyllifolia*	linalool 30.29	pulegone 16.95	*p*-menthone 10.27	menthone 7.83	1,8-cineole 6.72
[72]*brachycalyx*	linalool 39.92	piperitenone 31.93	pulegone 9.47	1,8-cineole 7.09	menthone 2.02
[73]No report July 2010	pulegone 30.41	limonene 15.64	menthalactone 10.28	menthone 7.39	menthol 5.27
[73]No report October 2010	menthalactone 33.89	pulegone 13.35	piperitone 13.35	guaiacol 9.97	menthone 5.13
[74]*serpyllifolia*	pulegone 58.50	*neoiso*-menthol 8.70	caryophyllene 3.90	isomenthone 3.90	α-terpinene 3.70

2) There is a clear majority of menth-sub-unit derived compounds as shown in Figure 3. See also closely related compounds shown in figure 1: pulegone, isomenthone and piperitenone-oxide (isomer).3) The variety in chemical composition and concentration of each ingredient is very wide.

Taking the example of *M. fruticosa* ssp. *Serpyllifolia*, Table 2, mentioned unde**r the** references 69, 71, 72, 74, differences are found in the five componds with highest concentrations and the differences continue for the other compounds. Moreover, in the cited references the differences continue with materials that have lower concentrations, and sometimes, a compound reported in one reference as having significant concentration does not exist at all in other reference. In most cases, these differences are related to localities of plant collection and seasonal variety (see below). Obviously, the type of subspecies has great effect on the chemical composition, and it is clearly shown in reference 72.

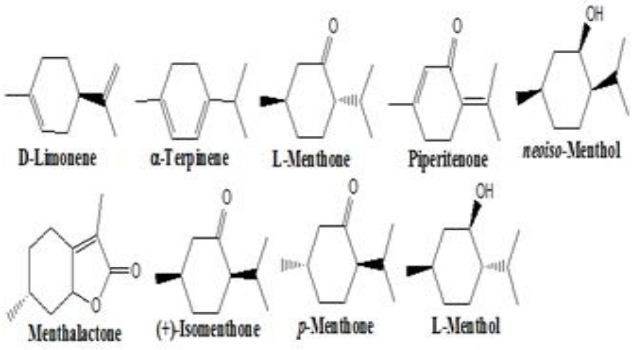

Figure 3. Menth-sub-unit-derived major compounds in *M. fruticosa*

The seasonal effect on the chemical compositions of *M. persica*, reported in reference 59, is significant since it is related to the sampling before and during the flowering season of the plant. In reference 73 there is no indication of the subspecies of *M. fruticosa* that was analyzed, but the seasonal differences are very large.

Seasonal effect on plant composition is well reported and in some cases, it can be almost controlled. For example, the three compounds with the highest concentrations in *Satureja cuneifolia* (Syn. *Micromeria spicata* Rchb.) analyzed in Lebanon, shows seasonal fluctuations in the concentration of each compound according to the development of plants over six months (June-November 2011).[75] The change in the concentration of each compound (*p*-cymene, γ-terpinene

As can be seen in Figure 3, *M. fruticosa* contains wide variety of natural products that can be used and utilized as starting materials for organic synthesis and drug development. However, many of these compounds are structural isomers or even stereoisomers (menthone and *p*-menthone are enantiomers). Isomer purity is one of the key requirements for successful organic synthesis and many studies are published about methods of isomer separation. In Table 1 and Table 2, pulegone is reported to have high concentration in micromeria subspecies. Its (1R)(+)-pulegone isomer is separated as pure enantiomer by Cyclodex B chiral capillary column.[77] Chiral column is also used for GC-MS analysis of *cis*- and *trans*-piperitone-oxide in *M. fruticosa* (and *Mentha longifolia*).[78] The findings of this research are interesting: Only enantiomerically pure laevo-rotatory piperitone oxides, (1*S*,2*S*,4*S*)-*trans*-piperitone-oxide and (1*S*,2*S*,4*R*)-*cis*-piperitone oxide, are detected by chiral analyses of *Micromeria fruticosa* (L.) Druce.

Table 3. Summary of the biological activities *M. fruticosa* compounds with highest concentrations.

*Traditional uses, if mentioned, are indicated in brackets.Considering the variability of the chemical composition of *M. fruticosa*, efforts were made to control the concentrations of some biologically active compounds in the plant. One of these studies found clearly that artificial modification of growth conditions, mainly light hours, has negligible effect on the chemical composition of the plants, especially the monoterpene content.[76] On the contrary, the same study found that the stage of maturation has the largest effect on monoterpene content of the leaves of *M. fruticosa*. For example, the content of pulegone can be as high as 80% of the essential oil in summer time (August), and drops drastically in the winter.

Active material	**Biological activities***
[71]Essential oil;methanolic extract	Antimicrobial; antioxidant (Herbal tea, mint substitute, sedative, anaesthetic, antiseptic, abortifacient, antirheumatic, CNS-stimulant, treatment of heart disorders and colds)
[74]Essential oil;aqueous extract	Both: antitumor. Aqueous extract: analgesic (Treatment of abdominal pains, diarrhea, eye infections, heart disorders, elevated blood pressure, colds and wounds)
[79]Essential oil	Insecticidal, synergism with other plants essential oils (same as first row)
[80]Acetone extract	Antibacterial, acaricidal, synergism with other plants extracts (Given but not specified for single plant)
[81]Essential oil	Insecticidal, synergism with other plants essential oils (same as first row)
[82]Roots	Allelopathic: chemicals released by living plant's roots in soil
[83]Methanolic extract	Anti-inflammatory, myeloperoxidase inhibition (Abdominal pains relief, diarrhea, eye infections, heart disorders, high blood pressure, weariness, exhaustion, colds and open wounds)
[84]Essential oil	Anti microbial. Clear synergistic effect with standard antibiotics
[85]Aqueous extract	Anti-inflammatory, gastroprotective (Anti-inflammatory, wound healing, treatment abdominal pain and diarrhea)
[86]Essential oil	Anti-biofilm formation (streptococcus mutans), antimutagenic, antioxidant (Treatment of *stomach pain*, colic, uterine disorders, diarrhoea respiratory ailments,*coughs*, and colds)
[87]Ethanolic extract	Animicrobial, antioxidant (Treatment of abdominal pains, diarrhea, colds, wounds and skin infections)

The occurrence of the *cis*- and *trans*-piperitone-oxides is dependent on the population of the species. In all cases (1*S*,2*S*,4*S*)-*trans*-piperitone-oxide is detected together with (4*S*)-piperitone, while (1*S*,2*S*,4*R*)-*cis*-piperitone-oxide is detected together with (4*R*)-piperitone.

Biological activities of *M. fruticosa*

Many of the reported findings about the biological activities of *M. fruticosa* are similar to those of other subspecies. But since *M. fruticosa* is thoroughly studied, some reports present interesting results that were not reported for other subspecies (see **Table 3** below). Most articles that report findings of modern research of the biological activities of the plant, give some information about the traditional medical uses of folk medicines. Whether this linkage is evident or not, the results of modern researches are of high significance for modern medicine and drug discovery. This statement is supported by the large number of natural products found in *M. fruticosa* and on the diverse biological activities that the plant and its ingredients have. The findings of modern researches are summarized in **Table 3** and the traditional uses of the plant, ~~hat were~~ mentioned in each reference, if any, is presented

D) Future inspirations

Plant based therapy has served humans since pre-historical era. In modern times, the study of medicinal plants and natural products has gone through intensive attention, and sometimes much less than that. The 2015 medicine Nobel prize is awarded to three scientists based on their pioneering achievements. These are based on drug discovery from natural products. This spirit and momentum of this excellence can and should inspire us, and the members of the micromeria family can provide us with many starting points.

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