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Review Article

Chemical Composition and Biological Activity of *Ziziphora clinopodioides* Essential Oil: A Review

Zeinab Mazarei [1,*]

[1]Department of Chemistry, Faculty of Sciences, Shahid Chamran University of Ahvaz, Ahvaz, Iran

[*]*Corresponding author*: Department of Chemistry, Faculty of Sciences, Shahid Chamran University of Ahvaz, Ahvaz, Iran. Email: z.mazarei@scu.ac.ir

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Abstract

Context: *Ziziphora clinopodioides* is a well-known aromatic and culinary species of the genus *Ziziphora*. It has been used in Iranian folk medicine for healing digestive issues and fever. Extensive studies have been published on the characterization of the essential oil of this aromatic plant and its related biological properties. This study aimed to review the chemical composition and biological properties of *Z. clinopodioides* essential oil.
Evidence Acquisition: The literature survey was performed using search engines Google Scholar, Scopus, and PubMed, with the search period spanning within 1990 to 2022.
Results: The investigation of *Z. clinopodioides* essential oil composition revealed that oxygenated monoterpenoids, such as pulegone and related menthane-type structures, in addition to aromatic monoterpenoids, such as carvacrol and thymol, comprise the majority of *Z. clinopodioides* essential oil components. Due to the high monoterpenoid content, *Z. clinopodioides* essential oil possesses outstanding biological properties, including antibacterial, antifungal, and insecticidal activity.
Conclusions: *Ziziphora clinopodioides* essential oil could be considered a natural, rich source of bioactive monoterpenoids encompassing potent biological activities. Therefore, based on the reported properties, it seems that *Z. clinopodioides* essential oil potentially has widespread industrial applications.

Keywords: *Ziziphora clinopodioides*, Essential Oil, Monoterpenoids, Antibacterial Activity, Antifungal Activity

1. Context

Ziziphora is a genus of the *Lamiaceae* family, consisting of 17 aromatic herbs or subshrubs, which can be annual or perennial. These plants are found across Southern and Eastern Europe, North-West Africa, and Asia, extending to the Himalayas. *Ziziphora clinopodioides* Lam., known as "kakooti-koohi" in Persian, is one of the most well-known aromatic and edible species within this genus. It is widely distributed in Asia and Europe, especially in Turkey and the western regions of Iran (1).

Ziziphora clinopodioides is a highly branched perennial herb with stems that can reach a height of up to 50 cm. It features white to red-colored flowers. In Iran, there are nine subspecies of *Z. clinopodioides* (2). In traditional Iranian folk medicine, it has been used in the form of a decoction for various purposes, such as a stomach tonic, sedative, carminative, and antipyretic agent (3). Additionally, *Z. clinopodioides* is considered an effective remedy for various conditions, including cough, the common cold, bronchitis, headache, viral diseases, diarrhea, nausea, typhus, inflammation, edema, cardiovascular diseases, insomnia, diabetes, and asthma (4, 5). Furthermore, in Iran, the dried aerial parts of this plant are used as a spice to flavor food and beverages (6).

Essential oils are composed of volatile components found in aromatic plants and can be viewed as natural preservatives due to their high content of bioactive natural products, such as monoterpenoids. These essential oils also possess significant biological properties, including antimicrobial, antifungal, and antioxidant activity (7).

2. Evidence Acquisition

A review of the literature revealed that the chemical composition and biological properties of the essential oil of the aforementioned species have been investigated in various studies. This article compiles the major chemical constituents and categorizes the biological properties of *Z. clinopodioides* essential oil. The literature survey was conducted using search engines such as Google Scholar, Scopus, and PubMed. The search spanned within 1990 to 2022, and the inclusion criteria encompassed phytochemical components and reported biological activities of *Z. clinopodioides* essential oil.

3. Results

3.1. Essential Oil Composition

Table 1 provides a summary of detailed information regarding the essential oil composition of *Z. clinopodioide*s. Essential oil yields ranged from 0.1% to 4.5% based on the weight of dry plant material. Most of the plants studied were collected from various regions of Iran. Additionally, there are reports of plant species collected from China, Turkey, and other Asian countries listed in the table. The primary method employed for the extraction of *Z. clinopodioides* essential oil was hydrodistillation using a Clevenger-type apparatus. Although most researchers selected the aerial parts of *Z. clinopodioides* for essential oil extraction, a few studies also investigated the essential oil composition of leaves or the entire plant.

The compounds that comprised more than 10% of the total essential oil were listed in the table as major components. A general view apparently revealed that the essential oil of *Z. clinopodioides* could be considered a pulegone-rich essential oil. It is interesting to note that 45 out of 54 studies mentioned in Table 1 have identified more than 10% pulegone in *Z. clinopodioides* essential oil, and 37 studies reported more than 30% pulegone content. Two studies reported more than 80% pulegone content in *Z. clinopodioides* essential oil (16, 29). Various Biological activities have been reported for pulegone, antimicrobial, antifungal, insecticidal, anti-inflammatory, and gastrointestinal-related activity, to name a few (59). Therefore, one can reasonably predict that pulegone-rich essential oils possess outstanding biological effects.

Several studies reported relatively high amounts of aromatic monoterpenoids thymol (41.7 - 55.6 %) and carvacrol (54.3 - 74.3%) in the *Z. clinopodioides* essential oil as the main components. These two monoterpenoids have been known for their prominent antimicrobial properties. The structures of frequently identified compounds in the essential oil of *Z. clinopodioides* are represented in Figure 1. Most structures have menthane type skeleton, and due to their interesting structural similarity, it has been obviously understandable that the monoterpenoids biosynthetic pathway activated in the *Z. clinopodioides*. Oxygenated monoterpenes are more abundant than hydrocarbon monoterpenes in the *Z. clinopodioides* essential oil.

3.2. Biological Activities

A review of the literature regarding the biological properties of *Z. clinopodioides* essential oil revealed that most studies focused on its antibacterial effects (3, 6, 8, 10, 14, 17, 18, 28, 32, 49, 60-65), antifungal activity (10, 22, 44, 57, 66-73), and antioxidant capacity (9, 19, 28, 56, 64, 74, 75). A few other biological effects were assessed in some studies, which will be discussed later in this review. It is important to note that studies investigating the biological activity of formulations containing *Z. clinopodioides* essential oil have also been reviewed in this article to the extent that they have also examined the effect of pure essential oil.

3.2.1 Antibacterial Activity

The reported antibacterial effects of *Z. clinopodioides* essential oil are summarized in Table 2. An overview revealed that the most frequently studied gram-positive bacterial strains include *S. aureus*, *B. subtilis*, *L. monocytogenes*, *B. cereus*, and *S. epidermidis*. Additionally, the most studied gram-negative bacterial strains include *E. coli*, *K. pneumoniae*, and *S. typhimurium*. Most researchers evaluated the antibacterial effects of *Z. clinopodioides* essential oil using microdilution and disk-diffusion methods. It is evident that Z. clinopodioides essential oil exhibits significant antibacterial activity against both gram-positive and gram-negative bacteria, in addition to certain antibiotic-resistant bacterial strains.

However, considering the variations in subspecies, origins, and compositions of the essential oils, it can be expected that some differences might exist in the reported antibacterial activities. Additionally, variations in antibacterial treatment methods, such as the concentration of essential oil used in the disk-diffusion method, should be taken into account when comparing the data presented in Figure 1.

Although information regarding the composition of essential oil components is not available in a few reference articles, a general review indicates that essential oils containing high amounts of carvacrol (65 - 74%), thymol (41 - 55%), and pulegone (25 - 65%) have exhibited strong antibacterial effects. The carvacrol-rich (65.2%) *Z. clinopodioides* essential oil demonstrated prominent antibacterial activity against both gram-positive and gram-negative bacteria (8, 63). Considerable antibacterial effects were reported for *Z. clinopodioides* essential oil, containing 44.5% and 43.3% pulegone content, respectively (10, 17). Moreover, significant antibacterial activities were observed in carvacrol- and thymol-rich *Z. clinopodioides* essential oils (28). It has been proven that the antibacterial action of carvacrol and thymol is based on targeting the cytoplasmic membrane, resulting in

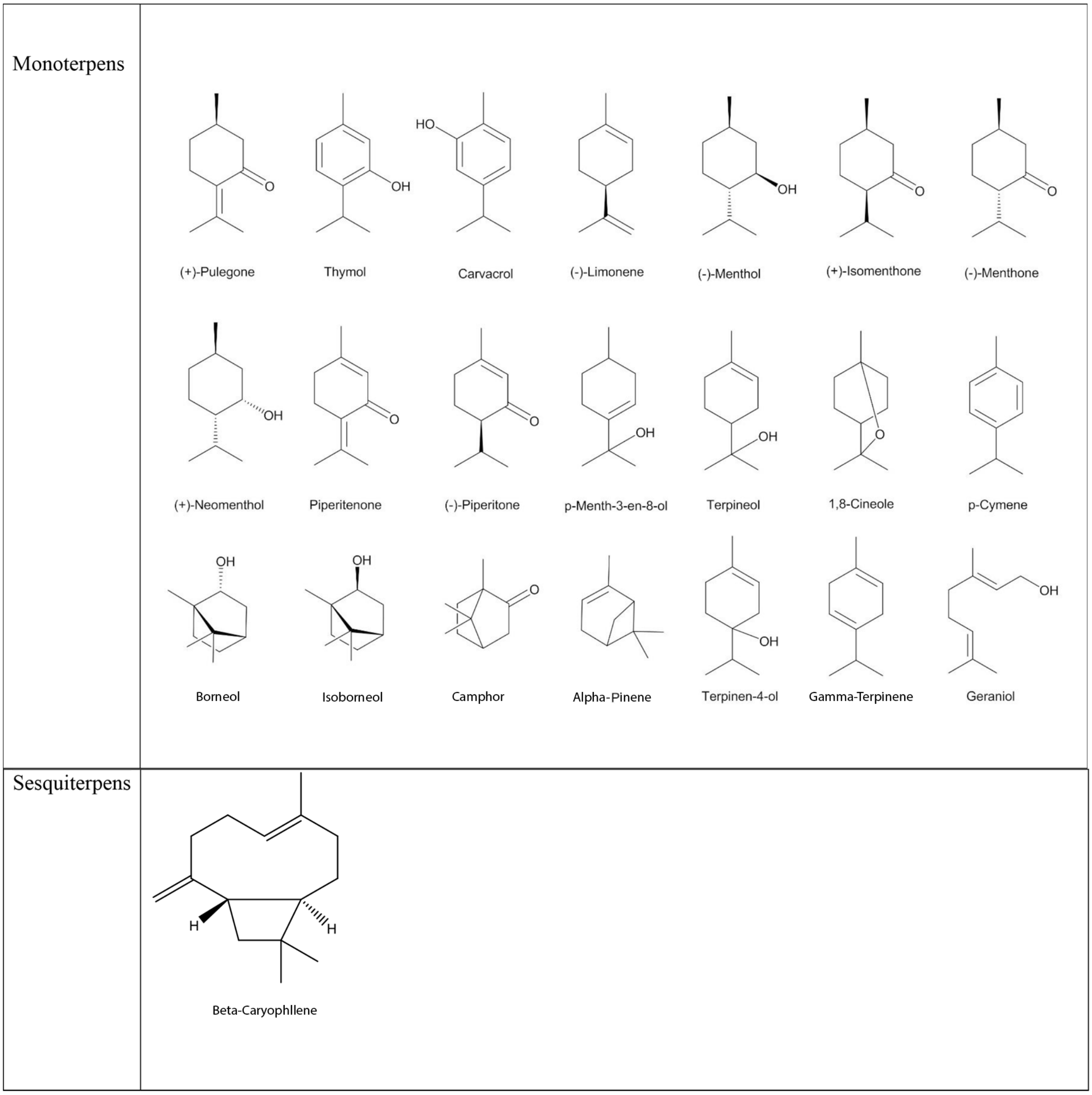

Figure 1. Chemical structures of key volatile components in *Ziziphora clinopodioides* essential oil

bacterial lysis and the leakage of intracellular contents (61, 62, 65). Considering that the antibacterial properties of the above-mentioned monoterpenoids have been widely studied and proven, it is not surprising that essential oils containing high amounts of these compounds exhibit strong antibacterial activity.

3.2.2 Antifungal Activity

The reported antifungal effects of *Z. clinopodioides* essential oil have been summarized in Table 3. A general overview revealed that the most studied fungi include several species of *Aspergillus* and *Trichophyton*. Most researchers assessed the antifungal activity of *Z. clinopodioide*s essential oil using broth macrodilution, broth microdilution, and mycelium inhibition methods. Predictable variations in the antifungal activity results of the represented studies have been observed due to differences in subspecies, origins, and essential oil compositions. Nevertheless, it is apparent that *Z. clinopodioides* essential oil exhibits significant antifungal activity. An evaluation of the composition of essential oils possessing antifungal activity listed in Table 2 revealed some extent of similarity to those with antibacterial effects. Distinguished antifungal effects have been reported for *Z. clinopodioides* essential oil, containing 54.4% Thymol content (57). In addition, notable antifungal activities were observed for *Z. clinopodioides* essential oils containing 53.5%, 44.5%, 37%, and 31.2% pulegone content (10, 22, 44, 72). Therefore, although not mentioned in these studies, the antifungal effects of carvacrol have been proven (71). Moreover, as supported by various published research based on the antifungal mechanism of action of thymol and pulegone (66-68), one would reasonably predict that the presence of high amounts of these monoterpenoids in *Z. clinopodioides* essential oil could also lead to strong antifungal effects.

[z] Abbreeviations: MFC, minimum fungicidal concentration; MIC, minimum inhibitory concentration.

3.2.3 Antioxidant Capacity

The reported antioxidant capacity of *Z. clinopodioides* essential oil has been summarized in Table 4. Most researchers assessed the antioxidant capacity of *Z. clinopodioides* essential oil using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method and β-carotene-linoleic acid bleaching assay. Examining the antioxidant results represented in Table 3 reveals that the total essential oil compounds should be considered in addition to the major components. As mentioned before, oxygenated monoterpenes make up the majority of *Z. clinopodioides* essential oil compounds. It has been proven that the presence of oxygenated monoterpenes and monoterpen hydrocarbons in the composition of essential oils leads to antioxidant activity (74, 75). Therefore, it is not unexpected that various *Z. clinopodioides* essential oils show different antioxidant activities due to the large variation in the percentage composition of the components. Therefore, the inhibition rate in the DPPH radical scavenging assay varies between 34 μg/mL and 5.12 mg/mL. However, due to the presence of oxygenated monoterpenes that comprise the majority of the essential oil components, *Z. clinopodioides* essential oil definitely possesses notable antioxidant activity.

3.2.4 Insecticidal Activity

The potential of *Z. clinopodioides* essential oil as an insecticidal agent has been discussed in a few studies. The lethal concentration 50 (LC50) value of pulegone-rich *Z. clinopodioides* Lam. essential oil was reported to be equivalent to 68.3 μL L-1 of air against *Tribolium castaneum* (43). In addition, the LC50 value of *Z. clinopodioides* essential oil against *Ephestia kuehniella* was reported as 47.95 μL L-1 of air and 0.94 mL.m-2 for fumigant and contact bioassay, respectively (76). The insecticidal activity of pulegone-rich *Z. clinopodioides* essential oil was assessed against *Ephestia kuehniella* Zeller, and the LC50 values of 54.61 and 1.39 μL L-1 of air were obtained for larva and adult insects (26). In another study, the pesticidal activity of *Z. clinopodioides* essential oil was assessed against *Plodia interpunctella*, and the LC50 values of 10.12 and 25.77 μL L-1 of air were obtained for larva and adult pests (77). The LC50 value of *Z. clinopodioides* Lam. essential oil against *Anopheles stephensi* and *Culex pipiens* was reported as 14.9 and 16.5 μg/mL, respectively (24). Therefore, *Z. clinopodioides* essential oil could be considered a natural agent possessing potential insecticidal properties.

3.2.5 Other Biological Properties

The antinociceptive activity of carvacrol-rich (65.2%) *Z. clinopodioides* essential oil was evaluated, and the obtained results demonstrated that this essential oil possesses antinociceptive effects, with the mechanism of action potentially involving an opioidergic pathway (78). In another study, the effect of using *Z. clinopodioides* essential oil and nisin as preservatives was assessed in relation to the sensory properties of fish burgers (79). The results revealed that adding *Z. clinopodioides* essential oil improved the odor, taste, and overall acceptability of the fish burgers.

Furthermore, the anti-inflammatory activity of *Z. clinopodioides* essential oil was assessed, and the half maximal inhibitory concentration (IC_{50}) values for soybean 5-lipoxygenase (5-LOX) inhibition were calculated as 33.12 μg/mL, confirming the moderate anti-inflammatory activity of the essential oil (64)).

4. Conclusions

Ziziphora clinopodioides is a well-known aromatic and medicinal herb of the genus Ziziphora. Extensive research has been undertaken on the chemical composition and biological properties of its essential oil. A comprehensive review of all published literature on the essential oil composition of this species reveals that oxygenated monoterpenoids, such as pulegone and other menthane-type structures, in addition to aromatic monoterpenoids, such as carvacrol and thymol, comprise the majority of *Z. clinopodioides* essential oil components. Due to the presence of high amounts of

Table 3. Antifungal Activity of Different *Ziziphora clinopodioids* Essential Oils

Species	Target Organism	Method	Result	References
***Z. clinopodioides* Lam.**	*A. niger, T. rubrum, T. reesei, M. gypseum*	Mycelium inhibition	Inhibition conc. (μL/mL) = 1, 0.5, 0.5, 0.5	(10)
***Z. clinopodioides* Lam.**	*S. sclerotiorum*	Mycelium inhibition	Contact condition: Inhibition conc. (μL/mL) = 1.25; Vapor phase condition: Inhibition conc. (μL/mL) = 0.15	(22)
		Germination inhibition	Contact condition: Inhibition conc. (μL/mL) = 1.00; Vapor phase condition: Inhibition conc. (μL/mL) = 0.15	
Z. clinopodioides	*A. flavus, A. parasiticus*	Broth macrodilution	MIC (μg/mL) = 48.82, 48.82; MFC (μg/mL) = 781.25, 390.625	(73)
Z. clinopodioides	*A. fumigatus, A. flavus*	Broth macrodilution	MIC 90 (mg/mL) = 0.5, 0.25; MFC (mg/mL) = 1, 0.5	(70)
		Broth microdilution	MIC 90 (mg/mL) = 1.5, 1.5; MFC (mg/mL) = 3, 3	
***Z. clinopodioides* L.**	*B. cinerea*	Mycelium inhibition	Inhibition conc. (mL/L) = 1.00, 2.00	(69)
Z. clinopodioides	*A. flavus, A. parasiticus*	Mycelium inhibition	Inhibition conc. (μL) = 9.00	(44)
Z. clinopodioides	*A. parasiticus, A. fumigatus*	Broth macrodilution	MIC 90 (mg/mL) = 0.37, 0.43; MFC (mg/mL) = 1.2, 1.37	(72)
		Broth microdilution	MIC 90 (mg/mL) = 2.1, 1.5; MFC (mg/mL) = 5.5, 3.2	
Z. clinopodioides	*M. canis, M. gypseum, T. mentagrophytes, T. rubrum, T. schoenleinii*	Broth microdilution	MIC (μL/mL) = 0.01, 0.01, 0.03, 0.06, 0.01; MFC (μL/mL) = 0.03, 0.01, 0.03, 0.06, 0.01	(57)
		Mycelium inhibition	(150 ppm) Inhibition percentage = 59.1, 48.8, 28.2, 60.9, 100	

Table 4. Antioxidant Capacity of Different *Ziziphora clinopodioids* Essential Oils

Species	Method	Result	References
***Z. clinopodioides* Lam.**	DPPH [a]	IC_{50} [b] = 55.3 μg/mL	(9)
	β-catotene-linoleic acid	61.6 % inhibition	
Z. clinopodioides	DPPH	IC_{50} = 3.6 - 4.2 mg/mL	(19)
***Z. clinopodioides* Lam.**	DPPH	IC_{50} (mg/mL) = 0.30 - 0.56	(28)
	Ferric reducing power	EC_{50} (mg/mL) = 0.40 - 0.91	
	β-catotene-linoleic acid	EC_{50} (mg/mL) = 0.09 - 0.23	
***Z. clinopodioides* var. rigida**	DPPH	IC_{50} = 33.94 - 61.48 μg/mL	(56)
	β-catotene-linoleic acid	108.69 % inhibition	
***Z. clinopodioides* Lam.**	DPPH	IC_{50} = 5.12 mg/mL	(64)
	ABTS [c]	IC_{50} = 0.79 mg/mL	
	FRAP [d]	66.9 μM Fe(II)/mg	

[a] 2,2-diphenyl-1-picrylhydrazyl
[b] IC_{50}: half maximal inhibitory concentration
[c] 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
[d] Ferric ion reducing antioxidant power

bioactive monoterpenoids in the essential oil, it has shown outstanding antibacterial properties against both gram-positive and gram-negative bacteria and several drug-resistant bacterial strains. Similarly, it seems that the bioactive monoterpenoids are responsible for the significant antifungal activity of *Z. clinopodioides* essential oil. The antioxidant capacity and insecticidal activity of *Z. clinopodioides* essential oil have been proven in several studies. Therefore, *Z. clinopodioides* essential oil could be considered a natural bioactive product possessing various biological properties. However, due to the lack of studies concerning its safety, it is suggested that further research is needed for future industrial usage of *Z. clinopodioides* essential oil.

Footnotes

Authors' Contribution: All stages of the research were carried out by the corresponding author.

Conflict of Interests: There was no conflict of interest to declare.

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Table 1. Characteristics of Different *Ziziphora clinopodioides* Essential Oils

Species Name	Origin	Part Used	Extraction Method	Major Components (> 10%)	% Yield	References
Z. clinopodioides	Kermanshah, Iran	Leaves	HD	Carvacrol (65.2), Thymol (19.5)	0.65 [a]	(8)
***Z. clinopodioides* subsp. Bungeana (Juz.) Rech. f.**	Khorasan, Iran	Aerial parts	HD	Pulegone (65.2), Isomenthone (11.9)	1	(6)
***Z. clinopodioides* subsp. rigida (BOISS.) RECH. f.**	Tabriz, Iran	Aerial parts	HD	Pulegone (45.8),k Pipertenone (17.4), p-Menth-3-en-8-ol (12.5)	1	(3)
***Z. clinopodioides* Lam.**	Lorestan, Iran	Aerial parts	HD	Pulegone (30.1), Thymol (21.3), p-Menth-3-en-8-ol (12.9)	1.4	(9)
***Z. clinopodioides* Lam.**	Khorasan Razavi, Iran	Aerial parts	HD	Pulegone (44.5), Terpineol (14.5), Methyl acetate (10.9)	0.75	(10)
***Z. clinopodioides* Lam.**	Ankara, Turkey	Aerial parts	HD	Pulegone (21.9), 1,8-Cineole (14.0)	0.33	(11)
Z. clinopodioides	Yovon, Tajikistan	Aerial parts	HD	Pulegone (35.0 - 72.8), Neomenthol (23.1), Menthone (13.3)	0.7 – 0.8	(12)
***Z. clinopodioides*Lam.**	Lorestan, Iran	Aerial parts	HD	Pulegone (30.1 - 44.6), Thymol (up to 21.3), p-Menth-3-en-8-ol (10.5 - 12.9), 1,8-Cineole (up to 10.4), Isomenthone (up to 11.6)	0.65-1.1	(13)
Z. clinopodioides	Erzurum-Palandoken Mountain, Turkey	Aerial parts	HD	Pulegone (31.9), 1,8-Cineole (12.2), Limonene (10.5)	0.44	(14)
***Z. clinopodioides*ssp. rigida**	Hamedan, Iran	Aerial parts	HD	Pulegone (0.7 - 44.5), 1,8-Cineole (2.1 - 26), Neomenthol (2.5 - 22.5)	–	(15)
Z. clinopodioides	Tacheng,Terks of the Yili region, China	Whole plant	HD	Pulegone (32.5 - 86.4), p-Menthanone (3.2 - 43.7)	–	(16)
***Z. clinopodioides*Lam.**	Kerman, Iran	Aerial parts	HD	Pulegone (43.3), Piperitenone (15.1)	0.96	(17)
Z. clinopodioides	East-Azerbaijan, Iran	Aerial parts	HD	Pulegone (25.9), 1,8-Cineole (19.7)	–	(18)
Z. clinopodioides	Coruh Valley, Turkey	Aerial parts	HD	Pulegone (41.1 - 51.1)	–	(19)
Z. clinopodioides	North Khorasan, Iran	Aerial parts	HD	Pulegone (40.1), Menthone (13.8), Isomenthone (12.3)	1	(20)
Z. clinopodioides	Kashan, Iran	Leaves	HD	Thymol (45.5)	–	(21)
***Z. clinopodioides*Lam.**	Xinjiang Uyghur Autonomous, China	Aerial parts	HD	Pulegone (53.5), Isomenthone (10.4)	1.2	(22)
Z. clinopodioides	Mazandaran, Iran	Aerial parts	HD	1,8-Cineole (10.4)	0.98	(23)
***Z. clinopodioides*Lam.**	North of Iran	Aerial parts	HD	Pulegone (36.4), Piperitenone (19.1)	0.9	(24)
***Z. clinopodioides*Lam.**	R. Chubai-Nura, Kazakhstan	–	HD	Pulegone (62.4)	–	(25)
***Z. clinopodioides*Lam.**	Iran	Aerial parts	HD	Pulegone (49.4), Piperitenone (10.7)	2.3-2.5	(26)
Z. clinopodioides	Alborz, Iran	Aerial parts	HD	Pulegone (58.8)	1	(27)
***Z. clinopodioides*Lam.**	Ilam, Lorestan, Kermanshah, Kurdestan, Iran	Leaf, flower, stem	HD	Carvacrol (65.1-74.3), Thymol (14.4 - 55.6), γ-Terpinene (24.4 - 24.6), p-Cymene (10.2 - 10.2)	0.1-4.5	(28)
***Z. clinopodioides*Lam.**	Urumq, China	Entire plant	HD	Pulegone (77.5 - 87.3), p-Menthanone (2.8-12.4)	1.1-1.8	(29)
***Z. clinopodioides*Lam.**	Charmahal va Bakhtiyari, Isfahan, Iran	Aerial parts	HD	Pulegone (17.5 - 57.8), p-Menth-3-en-8-ol (15 - 15.1), 1,8-Cineole (up to 27.4), Limonene (up to 12.8)	0.12-0.98	(30)

Z. clinopodioides**Lam.**	Baluchestan, Iran	Aerial parts	HD	Pulegone (61.7), cis-Caran-trans-2-ol (12.7), 1,8-Cineole (10.2)	1.86	(31)
Z. clinopodioides	North Khorasan, Iran	Aerial parts	HD	Pulegone (41.5), Piperitenone (18.5)	1.1	(32)
Z. clinopodioides	Golestan, Iran	Aerial parts	HD	Pulegone (7.3-16)	0.44-0.9	(33)
Z. clinopodioides	Erzurum, Turkey	Leaves	HD	Pulegone (60.2), Menthone (13.6), Menthol (10.9)		(34)
Z. clinopodioides	Tehran- Qazvin-Azarbaijan- Fars, Iran	Aerial parts	HD	Pulegone (23.0 - 52.0), 1,8-Cineol (up to 32.4), Limonene (up to 29.0), Neomenthone (up to 26.0), p-Menth-3-en-8-ol (up to 24.3), Piperitenone (up to 16.8), γ-Terpinene (up to 16.1)	0.13-1.44	(35)
Z. clinopodioides	Hamedan-Kurdestan, Iran	Aerial parts	HD	Pulegone (22.3 - 60.4), 1,8-cineol (up to 29.9), p-Menth-3-en-8-ol (up to 14.0), Piperitenone (up to 10.9), Neomenthol (up to 10.8), Isomenthone (up to 10.3), Terpinen-4-ol (up to 10.2)	0.37-1	(36)
***Z. clinopodioides* Lam.**	Iran	Aerial parts	Perculation (n-hexane fraction)	Pulegone (24.4), Menthol (14.0)	-	(37)
Z. clinopodioides	Iran	-	HD	Geraniol (20.6), Carvacrol (18.2)	-	(38)
Z. clinopodioides	Khorasan Razavi, Iran	-	SD	Pulegone (37), p-Piperitone (19.6)	-	(39)
Z. clinopodioides	Ermenek, Turkey	-	HD	α-Terpineol (up to 33.3), Camphor (10.9 - 12.4), Borneol (up to 24.4), α-Pinen (10.8 - 17.6), Isoborneol (up to 21.2)	0.12-0.5	(40)
***Z. clinopodioides* Lam.**	Kashan, Iran	Aerial parts	SDE, HD, SD, Ultrasonic	Pulegone (25.9 - 35.2), Piperitenone (10.1 - 27.9), Menthol (11.4-17.5)	0.3-1.3	(41)
***Z. clinopodioides* Lam.**	Fars, Iran	Aerial parts	HD	Pulegone (27.4), Isomenthone (10.1)	0.15	(42)
***Z. clinopodioides* Lam.**	Iran	Leaves	HD	Pulegone (51.8)	-	(43)
Z. clinopodioides	Kerman, Iran	-	HD	Pulegone (31.2), Menth-3-en-8-ol (23.8)	-	(44)
***Z. clinopodioides* subsp. Elbursensis; *Z. clinopodioides* subsp. Filicaulis**	Mazandaran, Tehran, Iran	Aerial parts	HD	Pulegone (21.5 - 38.9), Menthone (up to 10.4), Carvacrol (up to 16.6), Thymol (up to 10.1)	0.5-1	(45)
Z. clinopodioides	Van, Turkey	Aerial parts	HD	Pulegone (29.3), Menthone (21.8), 1,8-Cineole (15.3)	-	(46)
***Z. clinopodioides* subsp. bungeana (Juz.)**	Khorasan, Iran	Aerial parts	HD	Pulegone (20.2 - 34.2), Iso-menthone (9.1-18.3)	0.23-0.61	(2)
***Z. clinopodioides* Lam.**	Fars, Iran	Aerial parts	HD	Pulegone (26.3 - 50.9), p-Menth-3-en-8-ol (11.3 - 14.7), Menthone (10-10.4)	0.2-1.2	(47)
***Z. clinopodioides* Lam.**	Iran	Aerial parts	HD	Pulegone (23.1), Menthone (19.5), p-Menth-3-en-8-ol (10.4)	-	((48)
Z. clinopodioides	Tehran, Iran	Aerial parts	HD	Thymol (41.7)	-	(49)
***Z. clinopodioides* Lam.**	North Khorasan, Iran	Aerial parts	HD	Pulegone (46.1), Menthol (10.7)		(50)
Z. clinopodioides	Bojnurd, Iran	Aerial parts	HD	Pulegone (26.6), Iso-menthone (17.5), Limonene (10.5)	1.5	(51)
***Z. clinopodioides* Lam.**	Hamedan, Iran	Aerial parts	HD	Pulegone (59.3), β-caryophyllene (10.4)	-	(52)
Z. clinopodioides	Mazandaran, Iran	-	HD	Pulegone (48.2), 1,8-cineol (11.2)	-	(53)
Z. clinopodioides	Alborz, Iran	Aerial parts	HD	Carvacrol (54.3), Thymol (12.5)	2.5	(54)
Z. clinopodioides	Iran	-	-	Pulegone (79.3)	-	(55)

***Z. clinopodioides* Var. rigida**	Kerman, Iran	Aerial parts	HD	Pulegone (52.4), Dihydrocarvyl acetate (14.1), 1,8-cineole (13.0)	-	(56)
Z. clinopodioides	Urmia, Iran	Aerial parts	HD	Thymol (54.4)	-	(57)
Z. clinopodioides	Kordestan, Iran	-	HD	Thymol (34.2), Pulegone (14.4), Carvacrol (10.9)	0.8	(58)

Abbreviations: HD, hydrodistillation; SD, steam distillation; SDE, simultaneous distillation-extraction.
[a] Fresh plant material

Table 2. Antibacterial Activity of Different *Ziziphora clinopodioides* Essential Oils

Species	Target Organism	Method	Result	References
Z. clinopodioides	*S. aureus, B. subtilis, B. cereus, L. monocytogenes, S. typhimurium, E. coli O157:H7*	Microdilution	MIC (μL/mL) = MBC = 0.0025, 0.0012, 0.0012, 0.0012, 0.0025, 0.0025	(8)
	S. aureus, B. subtilis, B. cereus, L. monocytogenes, S. typhimurium, E. coli O157:H7	Agar disk diffusion (20 μL/disk)	IZ (mm) = 30, 23, 23, 28, 22, 26	
***Z. clinopodioides* subsp. bungeana (Juz.) Rech. f.**	*B. subtilis, S. epidermidis, S. aureus, E. faecalis, K. pnemoniae, E. coli*	Microdilution	MIC (mg/mL) = 3.75, 3.75, 3.75 , > 15, >15, 3.75	(6)
	B. subtilis, S. epidermidis, S. aureus, E. faecalis, K. pnemoniae, E. coli	Disk diffusion (10 μL/disk)	IZ (mm) = 20, 22, 19, 14, 11, 20	
***Z. clinopodioides* subsp. rigida (BOISS.) RECH. f.**	*B. subtilis, S. epidermidis, S. aureus, E. faecalis, K. pnemoniae, E. coli*	Microdilution	MIC (mg/mL) = 3.8, 7.5, 7.5, >15, 15, 15	(3)
	B. subtilis, S. epidermidis, S. aureus, E. faecalis, K. pnemoniae, E. coli	Disk diffusion (15 μL/disk)	IZ (mm) = 18, 16, 15, 12, 11, 15	
***Z. clinopodioides* Lam.**	*E. coli, K. pnemoniae, S. aureus, P. aeruginosa, S. typhi*	Microdilution	MIC (%V/V dilution) = 0.003, 0.067, 0.033, 0.033, 0.067	(10)
Z. clinopodioides	(total 52 bacterial strains) *B. sphaericus, B. flexus, C. ammoniagenes, E. sakazakii, X. arboricola corylina*	Disk diffusion (10 μg/disk)	IZ (mm) = 27, 25, 25, 24, 24,	(14)
	(total 35 bacteria) *E. faecalis, M. catarrhalis, E. hormaechei, E. acetylicum, C. ammoniagenes, B. subtilis, B. marinus,*	Microdilution	MIC (μg/mL) = 7.81, 7.81, 15.60, 15.60, 15.60, 15.60, 15.60	
***Z. clinopodioides* Lam.**	*S. enterica, B. cereus, E. aerogenes, S. aureus, L. monocytogenes*	Disk diffusion (10 μg/disk)	IZ (mm)= 19.3, 20.3, 19, 14, 32.1	(17)
	S. enterica, B. cereus, E. aerogenes, S. aureus, L. monocytogenes	Microdilution	MIC (μg/mL) = 0.25, 1, 0.25, 0.5, 0.125	
	S. enterica, E. aerogenes, S. aureus, L. monocytogenes		MBC (μg/mL) = 2, 2, 0.5, 0.125	
Z. clinopodioides	Antibiotic resistant *S. aureus*	Disk diffusion (50, 100 μL)	IZ (mm) = 0.81, 0.18	(18)
Z. clinopodioides	*S. aureus, B. subtilis, B. cereus,L. monocytogenes, S. typhimurium, E. coli O157:H7*	Microdilution	MIC (μL/mL) = 0.0003, 0.0003, 0.0004, 0.0003, 0.0004, 0.0004	(63)
***Z. clinopodioides* Lam.**	*S. aureus*	Microdilution (%V/V dilution)	MIC = 0.03 - 0.04 ; MBC = 0.04 - 0.05	(28)
	B. subtilis		MIC = 0.03 - 0.04; MBC = 0.03 - 0.05	
	B. cereus		MIC = 0.04 - 0.05; MBC = 0.05	
	L. monocytogenes		MIC = 0.03 - 0.04; MBC = 0.03 - 0.04	
	S. typhimurium		MIC = 0.04 - 0.05; MBC = 0.05 - 0.06	
	E. coli O157:H7		MIC = 0.04 - 0.05; MBC = 0.05	

	S. aureus	Disk diffusion (20 μL/disk)	IZ (mm) = 28.4 - 33.3	
	B. subtilis		IZ (mm) = 20.2 - 28.4	
	B. cereus		IZ (mm) = 21.4 - 28.1	
	L. monocytogenes		IZ (mm) = 26.2 - 32.4	
	S. typhimurium		IZ (mm) = 18.3 - 23.1	
	E. coli O157:H7		IZ (mm) = 23.1 - 27.4	
Z. clinopodioides	*S. aureus, B. cereus, K. pnemoniae, E. coli*	Microdilution	MIC (μg/mL) = 4.25, 1.25, 7.25, 5.75; MBC (μg/mL) = 90, 4.50, 7.25, 5.75	(32)
Z. clinopodioides	*L. acidophilus, B. bifidum*		Lethal dose (ppm) = 1750, 1500	(49)
***Z. clinopodioides* L.**	*S. aureus, S. epidermidis, S. saprophyticus, E. coli, K. pnemoniae, P. vulgaris, E. aerogenes, C. frundii, P. areuginosa*	Disk diffusion (30 μL/disk)	IZ (mm) = 22, 20, 21, 21, 29, 19, 19, 20, 5	(60)
***Z. clinopodioides* Lam.**	*E. coli, MRSA*	Microdilution	MIC (mg/mL) = 5, 10; MBC (mg/mL) = 5, 10	(64)

Abbreviations: MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration, IZ, inhibition zone.