REVIEW ARTICLE

Special Issue-Lamiaceae Family: Phytochemistry, Pharmacology, Ethnopaharmacology, Ethnobotany and as Food Soruce

A C G publications

Rec. Nat. Prod. 19:SI (2025) 375-399

records of natural products

An Updated Review on *Ziziphora* L.: A Valuable Source of Phytoconstituents for Potential Health Benefits

Mert Ilhan [1], Perihan Gürbüz [2] and İpek Süntar [3*]

[1]*Department of Pharmacognosy, Faculty of Pharmacy, Düzce University, 81620, Düzce, Türkiye*

[2]*Department of Pharmacognosy, Faculty of Pharmacy, Erciyes University, 38039, Kayseri, Türkiye*

[3]*Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, 06330, Ankara, Türkiye*

(Received April 17, 2025; Revised May 16, 2025; Accepted May 19, 2025)

Abstract: *Ziziphora* L. (Lamiaceae) is a genus of annual or perennial medicinal plants. These species are characterized by their aromatic features and are widely distributed across Southern and Eastern Europe, Asia, and North-West Africa. In Türkiye, the genus comprises eleven taxa, namely *Ziziphora clinopodioides* Lam., *Z. clinopodioides* subsp. *elbursensis*, *Z. clinopodioides* subsp. *filicaulis*, *Z. clinopodioides* subsp. *kurdica*, *Z. clinopodioides* subsp. *rigida*, *Z. capitata* L., *Z. persica* Bunge, *Z. tenuior* L., *Z. taurica* M.Bieb., *Z. taurica* Bieb. subsp. *taurica*, and *Z. taurica* Bieb. subsp. *cleonioides* (Boiss.) Davis. *Ziziphora* species have been used in Turkish, Kazakh, and Iranian folk medicine, especially in the form of infusion, decoction and maceration, owing to their antiseptic, expectorant, stomachic, carminative, and sedative effects. *Ziziphora* species have also been used against the common cold, coughing, migraine, fever, inflammation, diarrhea, and depression. There is a high number of studies documenting the phytochemical features and biological activities of *Ziziphora* species. Although the essential oil composition of the *Ziziphora* genus was the primary focus of earlier studies, these species also contain triterpenes, flavonoids, and phenolic acids. They were demonstrated to display antimicrobial, antioxidant, and immunomodulatory activities. Given their diverse biological activities and phytoconstituents, *Ziziphora* species represent a promising candidate for further pharmacological research. In the present review, ethnobotanical records, phytochemical profiles, and bioactivities of *Ziziphora* species will be extensively presented.

Keywords: Lamiaceae; *Ziziphora*; ethnobotany; biological activity; phytochemistry.

1. Introduction

Plant-based products continue to be a key element in primary healthcare, serving as a remedy in developing countries. As a result, the commercial development of medicinal plants as a new source of bioactive compounds for improving human health is of significant importance. There are numerous plant families and herbs recognized for their medicinal properties, with the Lamiaceae family being one of the most distinctive and largest worldwide [1]. In Türkiye, the Lamiaceae family ranks as the third largest, following the Asteraceae and Fabaceae families [2]. Lamiaceae is particularly noted for the essential oils produced by many of its members, as well as for the presence of diterpenoids [3]. *Ziziphora* L., a genus within the Lamiaceae family that includes species with medicinal features, is an essential representative of this family.

* Corresponding author:-E-Mail: ipesin@gazi.edu.tr

The article was published by ACG Publications
http://www.acgpubs.org/journal/records-of-natural-products June 2025 EISSN:1307-6167
DOI: http://doi.org/10.25135/rnp.523.2504.3496
Available online: June 28, 2025

Ziziphora is found across Central Europe, Mediterranean countries, East and West Asia, and North Africa, with 31 taxa [2]. The genus comprises eleven taxa in Türkiye, namely *Ziziphora clinopodioides* Lam., *Z. clinopodioides* Lam. subsp. *elbursensis* (Rech.f.) Rech.f., *Z. clinopodioides* Lam. subsp. *filicaulis* (Rech.f.) Rech.f., *Z. clinopodioides* Lam. subsp. *kurdica* (Rech.f.) Rech.f., *Z. clinopodioides* subsp. *rigida* (Boiss.), *Z. capitata* L., *Z. persica* Bunge, *Z. tenuior* L., *Z. taurica* M.Bieb., *Z. taurica* Bieb. subsp. *taurica*, and *Z. taurica* Bieb. subsp. *cleonioides* (Boiss.) P.H. Davis [4]. Among these, only *Z. taurica* subsp. *cleonioides* (Boiss.) is endemic to Türkiye [5].

Ziziphora species are annual except *Z. clinopodioides* [2]. The leaves of *Ziziphora* species are either short petiolate or sub-sessile, with glandular hairs. The glandular hairs accumulate and release a significant amount of essential oils, emitting a distinct, aromatic fragrance. The flowers are typically arranged in verticillasters, which may be scattered on leaf axils or concentrated in a terminal inflorescence. The size of floral leaves varies, with some being as large as the stem leaves, while others are reduced. The calyx is narrow and cylindrical, with 13 veins, villous texture, and an annulate throat. It is 2-lipped, with the upper lip having three teeth and the lower lip two. The corolla is 2-lipped, with a straight upper lip and a 3-lobed lower lip, the middle lobe being narrower than the lateral lobes. The anterior stamens are fertile and reach the upper corolla lip, while the posterior stamens are rudimentary or absent, with only one or two anther cells fully developed. The style apex is deeply cleft, and the posterior lobe is short. The fruit consists of smooth, ovoid nutlets [6]. The leaves, flowers, and stems are commonly used as wild vegetables or food additives to enhance flavor and aroma [7].

Numerous studies on the essential oils of *Ziziphora* species have identified pulegone as the most prevalent compound [8]. Other major components include limonene, 1,8 cineole, piperitenone, piperitone, menthol, and thymol. Studies have demonstrated that the essential oils of *Ziziphora* species possess antioxidant, antiseptic, and antibacterial properties [9-11]. Due to these beneficial properties, certain *Ziziphora* species are used in traditional medicine by local populations. Given their diverse biological activities and phytoconstituents, *Ziziphora* species represent a promising candidate for further pharmacological research. In fact, a number of patents have been issued for the use of *Ziziphora* species—specifically, *Z. bungeana* and *Z. clinopodioides*—in medicine. These consist of particular extraction processes, analytical methodologies, agricultural applications, and medicinal formulations (e.g., polyherbal skin care compositions, anti-inflammatory and hair health compositions, and oral care formulations) [6].

While review studies on members of the genus *Ziziphora* have been conducted in the past, they have either been restricted to Kazakh *Ziziphora* spp. or concentrated on *Z. clinopodioides* and essential oil of this genus. The current study sought to update any prior review studies by providing an overview and summary of the ethnobotanical uses, reported phytochemicals and biological activities from *Ziziphora* members in various habitats, concentrating solely on literature data from 1990 to 2025, due to the lack of pertinent review data in the literature.

2. Materials and Methods

All *Ziziphora* taxa are listed in this study using their most recent, recognized scientific names as listed in contemporary taxonomic databases [12, 13]. Scopus, PubMed, SciFinder, and Google Scholar were used for a detailed analysis of the phytochemical composition of the *Ziziphora* taxa. For data mining on phytochemical data, the search phrases "*Ziziphora* phenolic compounds", "*Ziziphora* polyphenols", "*Ziziphora* terpenoids", "*Ziziphora* constituents", and "*Ziziphora* phytochemicals" were used. The search phrases "*Ziziphora* pharmacology" and "*Ziziphora* ethnobotany" were used to obtain data on bioactivity tests and traditional use.

Table 1. Ethnomedicinal uses of *Ziziphora* species

Botanical name	Country	Parts used	Method of preparation	Traditional therapeutic use	References
Z. bungeana Juz.	Kyrgyzstan Uzbekistan	Aerial parts	Decoction	**As** antiarrhythmic, hypotensive, and cardiotonic; **to relieve** respiratory distress, dizziness	[6, 22]
Z. capitata L.	Türkiye	Leaves, aerial parts, whole plant	Infusion for internal use; decoction for extrenal use	**As** appetizer, stomachic; **to treat** cold, cough, respiratory tract diseases, diarrhea, and hemorrhoid.	[2, 23-28]
Z. clinopodioides Lam.	Eastern Balkan Peninsula,Central, southeast Asia, Middle East countries and some African countries	Leaves, aerial parts, whole plant	Infusion	**As** appetizer, anti-emetic, sedative, anti-inflammatory, expectorant, cardiotonic, carminative, stomachic, laxative, aphrodisiac, antipyretic, antiseptic; **to treat** headache, oedema, eye diseases, cold, cough, infectious diseases, viral diseases, typhus, nausea and vomiting, insomnia, respiratory tract diseases, hypertension, cardiovascular diseases, diabetes, diarrhea, and wounds.	[2, 20, 27, 29-39]
Z. hispanica L.	Spain	Aerial parts	Infusion	**As** digestive; **to treat** viral diseases	[40]
Z. pamiroalaica Juz.	Kyrgyzstan, Tajikistan	-	Tincture	**As** antiemetic, antiarhythmic, and antihypertensive; **to treat** headache, stomachache, gastritis, flu, cough, cold, angina, infections; **for** blood cleaning	[38, 41, 42]
Z. pedicellata Pazij & Vved.	Uzbekistan	Aerial parts	Tincture and decoction	**As** hypotensive, and diuretic; **for** wound-healing	[43]
Z. persica Bunge	Iran	Leaves	Infusion and decoction	**As** antipyretic, stomach tonic, cardiac tonic, and anxiolytic; **to treat** abdominal pain, flatulence, dyspepsia, and diarrhea	[1, 3, 44-46]
Z. tenuior L.	Türkiye and Iran	Leaves, aerial parts, whole plant	Infusion for internal use; decoction for external use	**As** analgesic, antipyretic, expectorant, stomachic, emmenagogue, and carminative; **to** treat eye diseases, cold, flu, respiratory tract diseases, hypertension, rheumatoid arthritis, uterus infection, gastritis, constipation, pyometra, rickets, cholelithiasis, enteritis, dysentery, infertility, abscess, wound and burn	[2, 25, 27-29, 38, 47-53]
Z. taurica M. Bieb. subsp. *taurica*	Türkiye	Leaves, aerial parts, whole plant	Infusion for internal use; decoction for external use	**As** stomachic, appetizer, carminative; **to treat** wounds and burns, hypertension, circulatory system disorders, cholesterol, cold, and diarrhea	[2, 25, 28, 31, 39, 54, 55]
Z. taurica M. Bieb. subsp. *cleonioides* (Boiss.) P.H.Davis	Türkiye	Leaves, aerial parts, whole plant	Infusion for internal use	**As** stomachic; **to relieve** headache, cold and flu	[2]

3. Ethnomedicinal Uses of *Ziziphora* Species

Ziziphora sp. are commonly known in Türkiye by various vernacular names such as "dağ reyhanı", "nane ruhu", "firüskül", "kır nanesi", and "karınağrısı otu". The aerial parts of these plants are traditionally used as vegetables, herbal teas, and flavoring agents in culinary preparations. In both Türkiye and Iran, *Ziziphora* species are widely employed in folk medicine, primarily in the form of infusions, for the treatment of colds and coughs, and are also used as carminatives, aphrodisiacs, sedatives, appetite stimulants, and for relieving stomach pain [11, 14-20]. Additionally, *Ziziphora* species have been utilized in the treatment of various ailments, including as antiseptics and wound-healing agents [21]. The traditional uses of *Ziziphora* species for the treatment of various ailments are commonly observed across Central and Southeast Asia and Middle Eastern countries, and are summarized in Table 1.

4. Phytochemistry of *Ziziphora* Species

The majority of phytochemical investigations conducted on *Ziziphora* species were primarily focused on their essential oil content. Regarding this numerous reviews and manuscripts on essential oil composition including factors affecting the yield, together with bioactivity of the essential oils have been published to date [56-58]. Thus, this review focuses on relatively less studied non-volatile secondary metabolites. In the current review almost 90 fully elucidated chemical structures from native *Ziziphora* (species and subspecies) have been reported over the last three decades (1990-2025). The compounds are categorized into chemical sub-groups, and their structures are provided as: (i) simple phenolics and phenolic acids & caffeic acid derivatives, (ii) flavonoids, and (iii) terpenoids. The retrieved publications relied on secondary metabolites that employed valid analytical methods notably UPLC-Q-TOF-MS and/or LC-MS/MS (compared with standard compounds), were included and mentioned with superscripts explained with footnotes in Table 2. The names of the compounds were given as the same in the manuscript (trivial or systematic names of some of the compounds were mentioned in parentheses). Stereochemistry of the compounds was not shown if it was not descriptive of the compounds.

4.1. Simple Phenolic Compounds, Phenolic Acids and Caffeic Acid Derivatives

Seventeen phenolic derivatives, 1-17 have been isolated from *Ziziphora* species, their structures, names and sources being shown in Table 2 and Figure 1.

4.2. Flavonoids

Forty flavonoids, 18-57 have been isolated from *Ziziphora* species, their structures, names and sources being shown in Table 2 and Figure 2. The data indicate that the majority of isolated flavonoids are flavon derivatives and as can be seen from Table 2, flavonoids are the dominant constituents within the genus *Ziziphora.*

4.3. Terpenoids

Twelve monoterpene derivatives (58-69), twelve triterpenes (70-81) and four other terpenoid derivatives (82-85) have been isolated and characterized from different *Ziziphora* species. Their structures, names and sources are shown in Table 2 and Figure 3. Megastigmane glycosides; blumenol C glucoside and blumenol C 9-*O*-(6'-*O*-malonyl-*β*-D-glucopyranoside) from *Z. clinopodioides* subsp. *bungeana*, isoprenoid derivated glycoside; erigeside B from *Z. clinopodioides* and a diterpene derivative jolkinolide E from Z. *clinopodioides* subsp. *bungeana* were classified under other terpenoid derivatives.

Table 2. Chemical constituents from the genus *Ziziphora*

No.	Compound class and name	Source	Ref.
	Phenolic Derivatives		
1	4-Hydroxyacetophenone (Piceol)	*Z. clinopodioides*	[59]
2	Acetovanillone (Apocynin)	*Z. clinopodioides*	[59]
3	3,4-Dihydroxybenzoic acid (Protocatechuic acid)	*Z. clinopodioides*	[36]
4	Ethyl *p*-coumarate	*Z. clinopodioides*	[59]
5	Caffeic acid (3,4-Dihydroxycinnamic acid)	*Z. pamiroalaica*	[41]
6	Ethyl caffeate	*Z. clinopodioides*	[33]
7	Caftaric acid (*trans*-Caftaric acid)	*Z. pamiroalaica*	[41]
8	Phaselic acid	*Z. pamiroalaica*	[41]
9	3-*O*-Caffeoylquinic acid (5-Chlorogenic acid)	*Z. pamiroalaica*	[41]
10	1,3-*O*-Dicaffeoylquinic acid	*Z. pamiroalaica*	[41]
11	4-*O*-*p*-Coumaroylquinic acid	*Z. pamiroalaica*	[41]
12	Rosmarinic acid	*Z. pamiroalaica*	[41]
		Z. clinopodioides	[36]
		Z. clinopodioides subsp. *bungeana*	[60]
13	Methyl rosmarinate (Rosmarinic acid methyl ester)	*Z. clinopodioides*	[61]
14	Chicoric acid (Dicaffeoyltartaric acid)	*Z. pamiroalaica*	[41]
15	Picein (*p*-Hydroxyacetophenone glucoside, Salinigrin, Piceoside)	*Z. clinopodioides*	[33, 62]
16	Benzyl alcohol glucoside	*Z. clinopodioides*	[33]
17	Phenylethyl 2-glucoside	*Z. clinopodioides*	[33]

Table 2. Chemical constituents from the genus *Ziziphora* (Continued)

No.	Compound class and name	Source	Ref.
	Flavonoids		
18	Chrysin	*Z. clinopodioides*	[59],[63]**
19	Baicalein	*Z. clinopodioides*	[36],[63]**
20	5,7-Dihydroxy-6-methoxyflavone (6-Methoxybaicalein)	*Z. bungeana*[a]	[64]*
21	Apigenin	*Z. tenuior*	[65]
		Z. clinopodioides	[33, 36, 59, 61, 62], [66]*
		Z. pamiroalaica	[41]
22	Genkwanin (Apigenin 7-methyl ether)	*Z. pamiroalaica*	[41]
23	Luteolin	*Z. clinopodioides*	[33, 36, 61]
		Z. pamiroalaica	[41]
24	Acacetin	*Z. clinopodioides*	[59, 61]
25	Diosmetin	*Z. clinopodioides*	[33]
26	Ladanein (Scutellarein 4',7-dimethyl ether)	*Z. pamiroalaica*	[41]
27	Thymusin	*Z. pamiroalaica*	[41]
28	5,6,4'-Trihydroxy-7,8,3'-trimethoxyflavone (Thymonin)	*Z. clinopodioides*	[59, 61]
29	8-Hydroxycirsiliol	*Z. pamiroalaica*	[41]
30	7-Methylsudachitin (8-Methoxycirsilineol)	*Z. pamiroalaica*	[41]
31	5-Demethylnobiletin	*Z. pamiroalaica*	[41]
32	5,7,3′-Trihydroxy-6,4′,5′-trimethoxyflavone	*Z. bungeana*	[64]*
33	5,4′-Dihydroxy-6-methoxy-7,8-methylenedioxyflavone	*Z. bungeana*	[64]*
34	Ziziphorin A	*Z. tenuior*	[65]
35	Ziziphorin B	*Z. tenuior*	[65]
36	Diosmin	*Z. clinopodioides*	[66]*,[63]**, [67]***
		Z. pamiroalaica	[41]
37	Acacetin-7-*O*-rutinoside (Linarin)	*Z. clinopodioides* subsp. *bungeana*	[60]
		Z. clinopodioides	[62], [66]*,[63]**
		Z. bungeana	[64]*
		Z. pamiroalaica	[41]
38	Apiin (Apigenin 7-*O*-*β*-D-apiofuranosyl (1→2)-*β*-D-glucopyranoside)	*Z. clinopodioides*	[67]***
39	5,7,2'-trihydroxyflavone 2'-*O*-glucopyranoside (Chrysin 2'-*O*-glucopyranoside)	*Z. clinopodioides*	[61, 62]

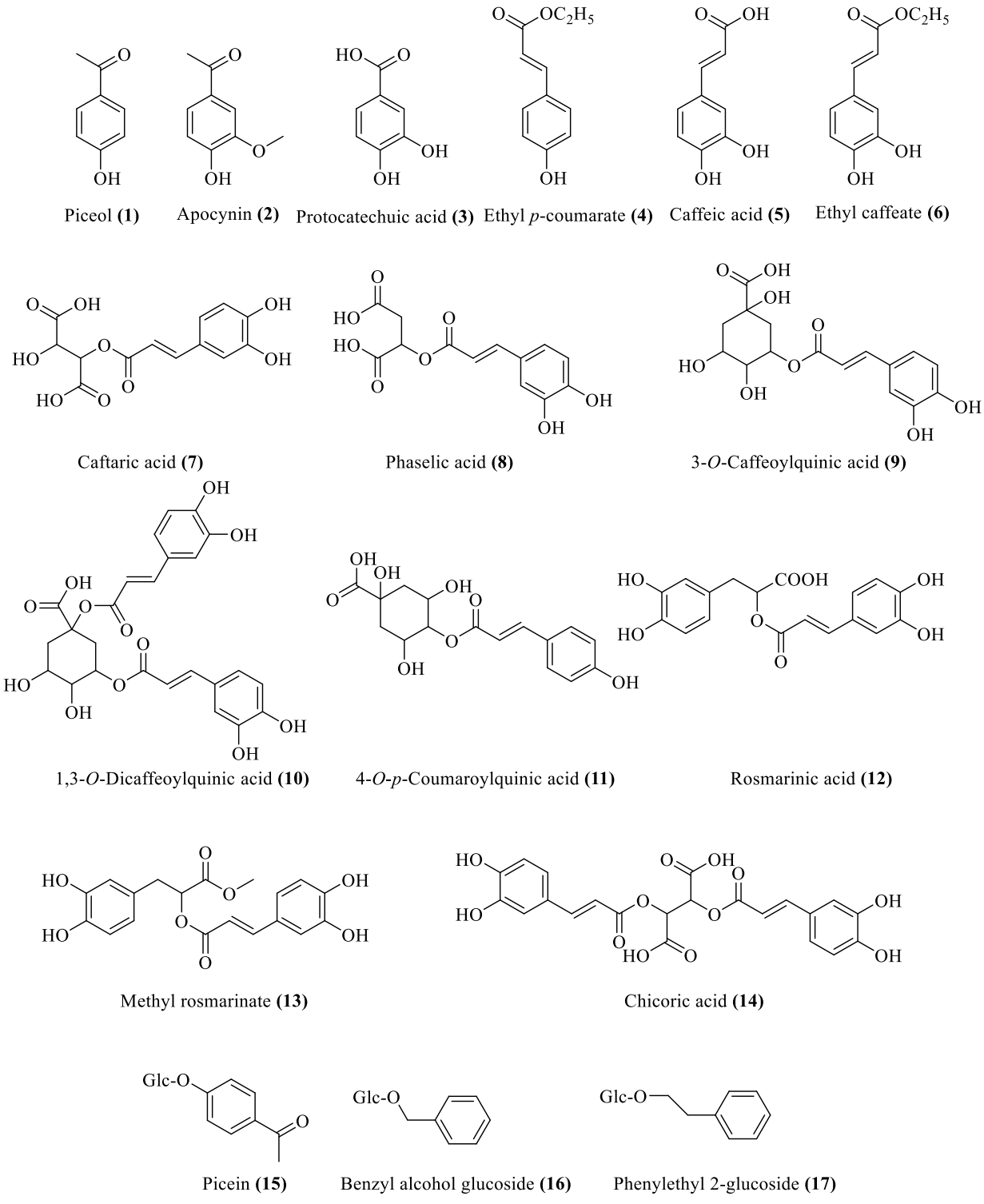
Table 2. Chemical constituents from the genus *Ziziphora* (Continued)

No.	Compound class and name	Source	Ref.
	Flavonoids **(**Continued)		
40	Apigenin 7-*O*-glucoside (Cosmosiin)	*Z. pamiroalaica*	[41]
41	Luteolin 7-*O*-glucoside (Cynaroside)	*Z. pamiroalaica*	[41]
		Z. clinopodioides	[67]***
42	Luteolin 7-*O*-glucronide	*Z. pamiroalaica*	[41]
43	Luteolin-7-*O*-rutinoside	*Z. clinopodioides* subsp. *bungeana*	[60]
44	Diosmetin 7-*O*-glucoside (Eridictiol)	*Z. pamiroalaica*	[41]
45	Pinocembrin-7-*O*-rutinoside	*Z. clinopodioides*	[36]
		Z. bungeana	[64]*
		Z. clinopodioides subsp. *bungeana*	[60]
46	Chrysin-7-*O*-rutinoside	*Z. bungeana*	[64]*
		Z. clinopodioides subsp. *bungeana*	[60]
		Z. pamiroalaica	[41]
47	Apigenin-4'-*O*-rutinoside	*Z. bungeana*	[64]*
48	Apigenin-7-*O*-rutinoside (Isorhoifolin)	*Z. bungeana*	[64]*
49	3'-Hydroxyacacetin-7-*O*-rutinoside	*Z. bungeana*	[64]*
50	Kaempferol	*Z. clinopodioides*	[63]**
51	Kaempferide (4′-Methylkaempferol)	*Z. clinopodioides*	[36]
52	Quercetin	*Z. clinopodioides*	[36]
53	Hyperoside (Quercetin 3-*O*-galactoside)	*Z. clinopodioides*	[63]**
54	Quercetin-3-*O*-glucoside (Isoquercitrin)	*Z. clinopodioides*	[63]**
55	Kaempferol-7-*O*-rutinoside	*Z. bungeana*	[64]*
56	Kaempferol-3-*O*-rutinoside	*Z. bungeana*	[64]*
57	Rutin	*Z. bungeana*	[64]*
		Z. clinopodioides	[63]**
		Z. clinopodioides subsp. *bungeana*	[60]
		Z. pamiroalaica	[68]

Table 2. Chemical constituents from the genus *Ziziphora* (Continued)

No.	Compound class and name	Source	Ref.
	Monoterpene derivatives		
58	Ziziphoric acid	*Z. clinopodioides* subsp. *bungeana*	[60]
59	7*α*-Hydroxymintlactone	*Z. clinopodioides* subsp. *bungeana*	[60]
60	7'-Hydroxypiperitone	*Z. clinopodioides* subsp. *bungeana*	[60]
61	Ziziphoroside A	*Z. clinopodioides*	[33]
62	Ziziphoroside B	*Z. clinopodioides*	[33]
63	Shizonepetoside A	*Z. clinopodioides*	[33]
64	9-*O*-glucopyranosyl-*p*-menthan-3-one	*Z. clinopodioides*	[33]
65	Shizonepetoside C	*Z. clinopodioides*	[33]
66	Ziziphoroside C	*Z. clinopodioides*	[33]
67	6'-Malonylziziphoroside A	*Z. clinopodioides* subsp. *bungeana*	[60]
68	Ziziphoroside D	*Z. clinopodioides* subsp. *bungeana*	[60]
69	Ziziphora diperoxy dimer	*Z. clinopodioides* subsp. *bungeana*	[69]
	Triterpenes		
70	Ursolic acid	*Z. clinopodioides*	[33]
		Z. clinopodioides subsp. *bungeana*	[69]
71	Pomolic acid (19*α*-Hydroxyursolic acid)	*Z. clinopodioides* subsp. *bungeana*	[69]
72	11-Oxoursolic acid	*Z. clinopodioides* subsp. *bungeana*	[69]
73	21*α*-Hydroxyursolic acid	*Z. clinopodioides* subsp. *bungeana*	[69]
74	Oleanolic acid	*Z. clinopodioides*	[33, 61]
		Z. clinopodioides subsp. *bungeana*	[69]
75	11-Oxooleanolic acid	*Z. clinopodioides* subsp. *bungeana*	[69]
76	3*β*-acetoxyolean-11-en-28,13*β*-olide	*Z. bungeana*	[70]
77	3*β*-acetoxy-11*α*,12*α*-epoxyoleanan-28,13*β*-olide	*Z. bungeana*	[70]
78	Maslinic acid	*Z. clinopodioides*	[33]
79	Betulin	*Z. clinopodioides* subsp. *bungeana*	[69]
		Z. bungeana	[70]
80	Betulinic acid	*Z. clinopodioides* subsp. *bungeana*	[69]
81	30-Hydroxybetulinic acid	*Z. clinopodioides* subsp. *bungeana*	[69]
	Other terpenoid derivatives		
82	Blumenol C glucoside	*Z. clinopodioides* subsp. *bungeana*	[60]
83	Blumenol C 9-*O*-(6'-*O*-malonyl-*β*-D-glucopyranoside)	*Z. clinopodioides* subsp. *bungeana*	[60]
84	Jolkinolide E	*Z. clinopodioides* subsp. *bungeana*	[69]
85	Erigeside B	*Z. clinopodioides*	[33]

[a]*Z. bungeana* is a synonym of *Z. clinopodioides* subsp. *bungeana*; It's mentioned how its stated in the manuscript. Studies which LC-MS/MS[*], UPLC-Q-TOF-MS[**], HPTLC[***] methodology were employed with superscripts.



Glc: Glucose

Figure 1. Structures of the phenolic derivatives from *Ziziphora* species

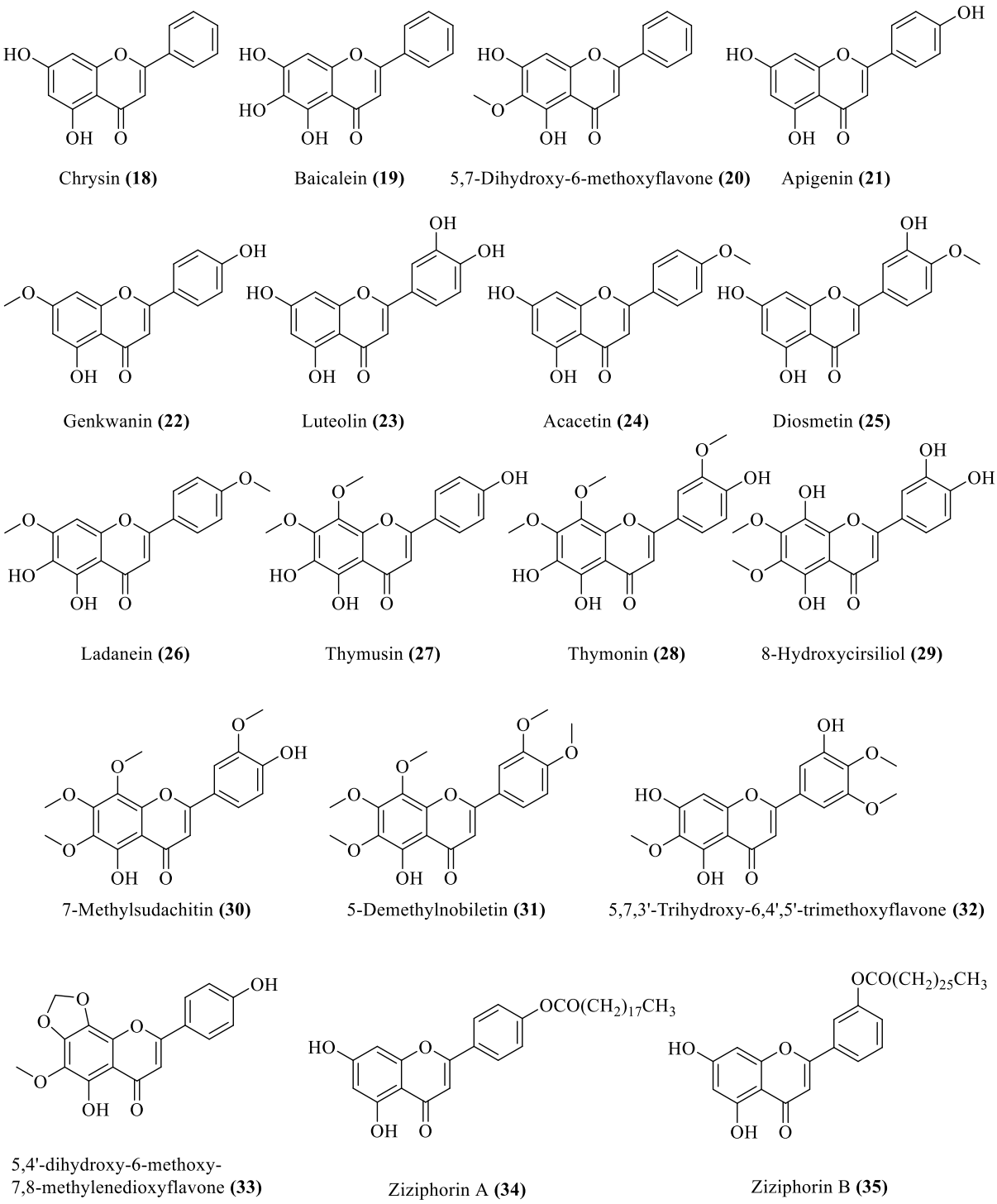


Figure 2. Structures of the flavonoid derivatives from *Ziziphora* species

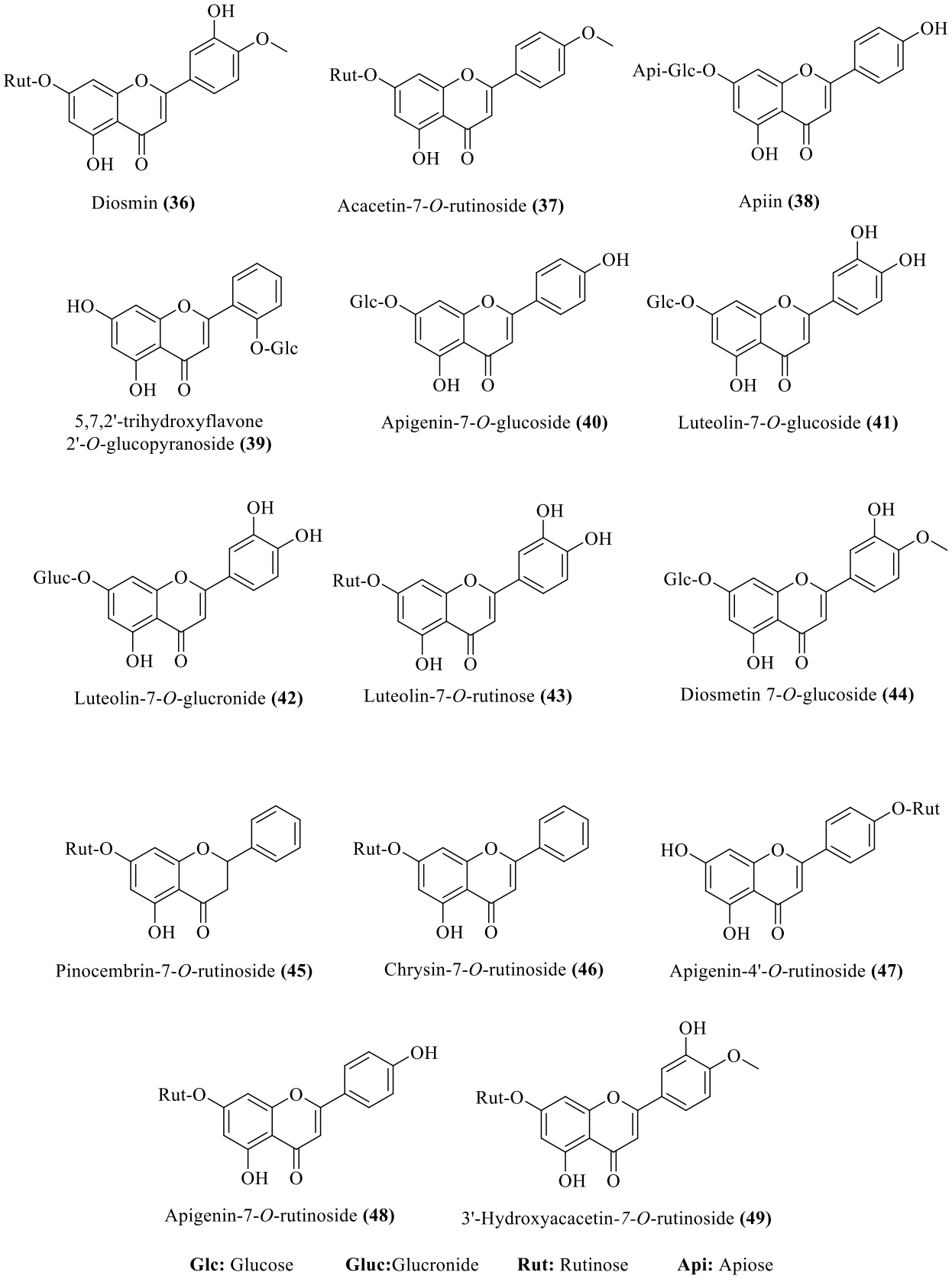


Figure 2. Structures of the flavonoid derivatives from *Ziziphora* species (Continued)

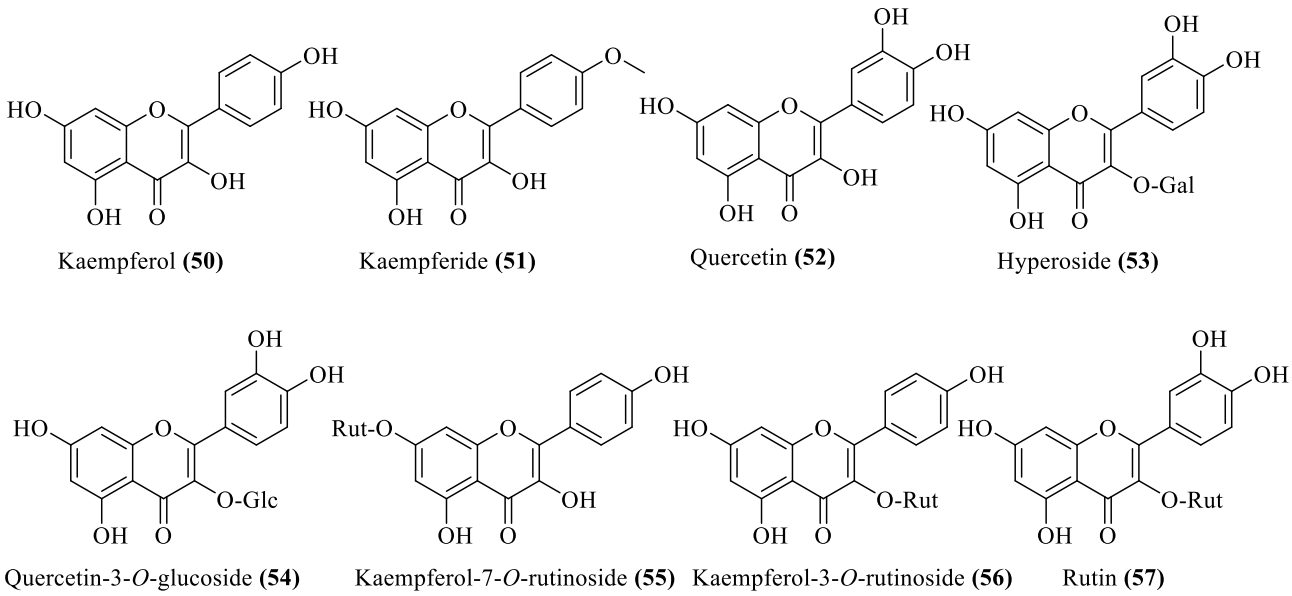
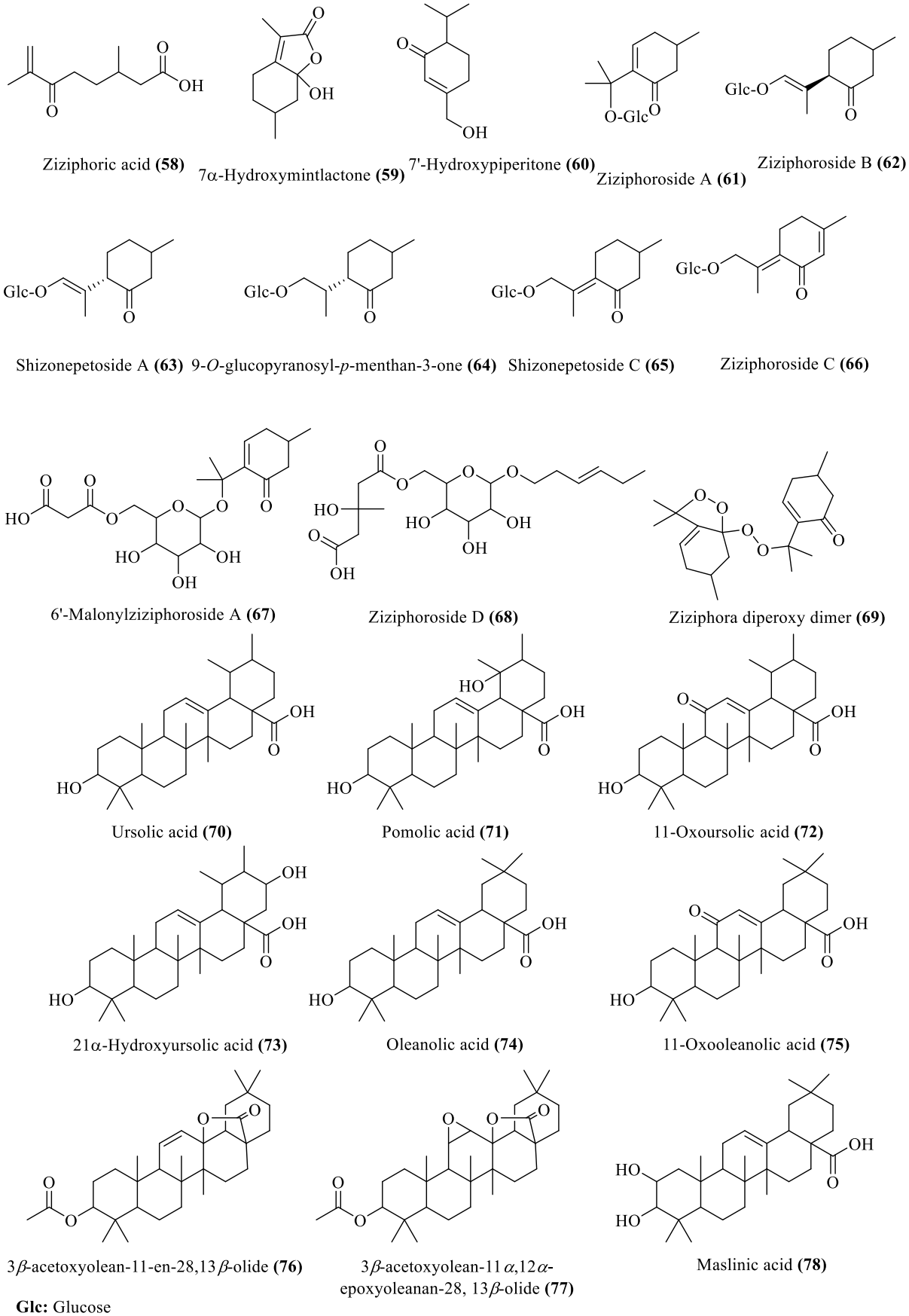
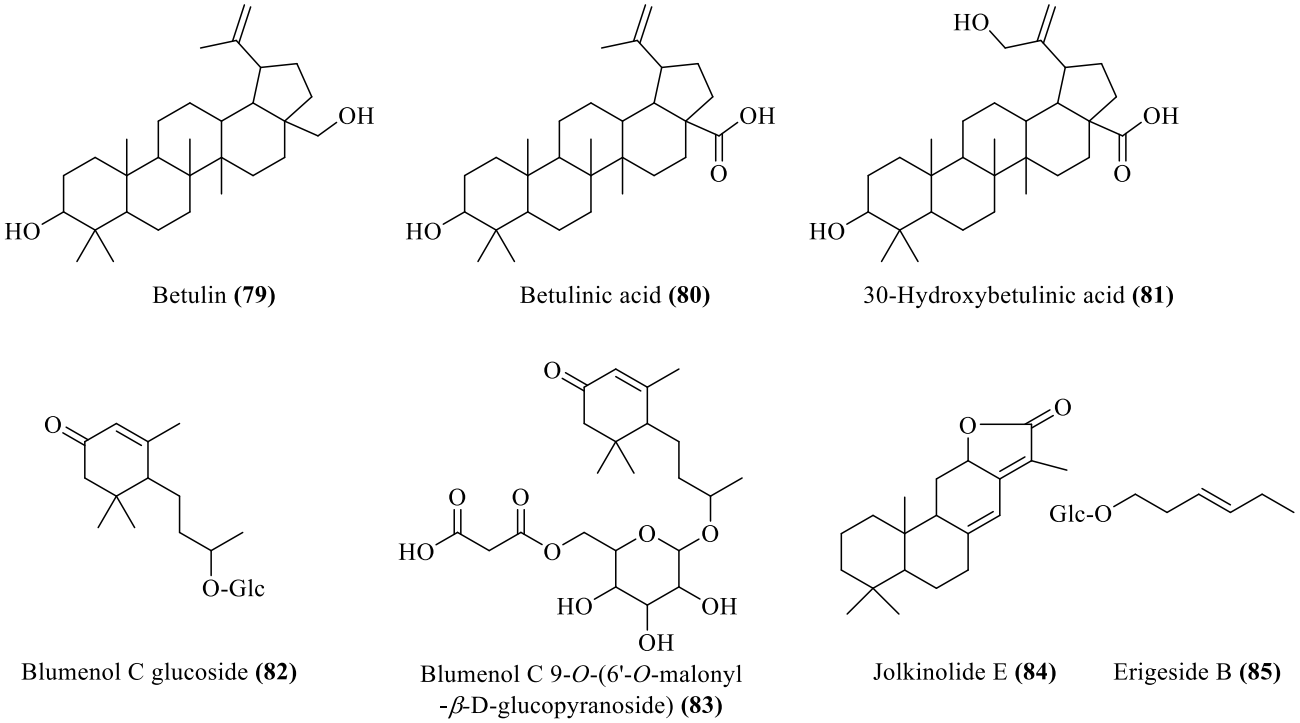


Figure 2. Structures of the flavonoid derivatives from *Ziziphora* species (Continued)



Glc: Glucose

Figure 3. Structures of the terpenoid derivatives from *Ziziphora* species



Betulin **(79)** | Betulinic acid **(80)** | 30-Hydroxybetulinic acid **(81)**

Blumenol C glucoside **(82)** | Blumenol C 9-*O*-(6'-*O*-malonyl -*β*-D-glucopyranoside) **(83)** | Jolkinolide E **(84)** | Erigeside B **(85)**

Glc: Glucose

Figure 3. Structures of the terpenoid derivatives from *Ziziphora* species (Continued)

5. Biological Activities of *Ziziphora* Species

Ziziphora species have a broad spectrum of biological activities that demonstrate their substantial therapeutic potential. These activities include antibacterial, antioxidant, cardiotropic, immunomodulatory, anti-inflammatory, cytotoxic, vasorelaxant, anti-atherosclerotic, insecticidal, and neuroprotective properties. Their historic therapeutic usage is supported by these studies, which also make *Ziziphora* a promising natural source for the discovery and development of new pharmacological substances. The biological activities of *Ziziphora* species investigated in various studies are summarized in Table 3.

Table 3. Biological activities of *Ziziphora* species

Plant	Biological Activitiy	Reference
Z. clinopodioides	Antibacterial and antifungal activities	[15, 30, 71]
	Antioxidant activity	[72, 73]
	Antiinflammatory activity	[74]
	Vasorelaxant activity	[59, 75]
	Anti-atherosclerotic activity	[76]
	Insecticidal activity	[77]
	Neuroprotective activity	[78]
Z. tenuior	Antibacterial and antifungal activities	[79, 80]
	Antioxidant activity	[80, 81]
	Antiinflammatory activity	[82]
	Immunomodulatory activity	[83]
Z. persica	Antibacterial activity	[7]
Z. taurica subsp. *cleonioides*	Antioxidant activity	[84]
Z. hispanica	Antioxidant activity	[85]
Z. clinopodioides subsp. *bungeana*	Cardiotropic activity	[60]
Z. capitata	Cytotoxic activity	[86]

5.1. Antibacterial and Antifungal Activities

Ozturk et al. investigated the antibacterial activity of the essential oil and methanol extract obtained from *Z. clinopodioides* and their chemical compositions. The antibacterial activity was tested against 52 Gram-positive and Gram-negative bacteria. The GC-MS studies identified 18 compounds, with (+)-pulegone (31.86%), 1,8-cineole (12.21%), limonene (10.48%), menthol (9.13%), *β*-pinene (6.88%), menthone (6.73%), piperitenone (5.30%), and piperitone (4.18%) being the primary constituents of the essential oils. In broth microdilution bioassays, the methanol extract and essential oil exhibited broad-spectrum antibacterial action against microorganisms. Maximum activity against *Acidovorax facilis*, *Bacillus xexus*, *Bacillus* spp., *Bacillus sphaericus*, *Brevibacillus brevis*, *Corynebacterium ammoniagenes*, *Enterobacter sakazakii*, *Erwinia carotovora*, *Moraxella catarrhalis*, and *Xanthomonas arboricola* was noted for both essential oil (>22mm) and methanol extract (>11mm) [15]. In a similar study, the essential oil constituents of *Z. clinopodioides* collected from Iran were extracted using hydrodistillation and examined using GC-MS. Twenty-seven compounds were found in the essential oil of the plant. Pulegone (44.5%), terpineol (14.5%), methyl acetate (10.9%), iso-neomenthol (7.1%), and 1,8-cineole (4.1%) were found to be major components of the essential oil. The antifungal and antibacterial activities of various concentrations of *Z. clinopodioides* essential oil were also assessed. The antifungal assays were performed using a poisoned food method against filamentous fungus namely *Aspergillus niger*, *Trichophyton rubrum*, *Trichoderma reesei*, and *Microsporum gypseum*. Antimicrobial assays were conducted against four Gram-negative bacteria, namely *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, and *Klebsiella pneumoniae* and one Gram-positive pathogen, namely *Staphylococcus aureus*, via a microdilution method. The essential oil demonstrated fungicidal properties at concentrations exceeding 1 µL/mL against *T. rubrum* and *M. gypseum*. The minimal inhibitory concentrations of the essential oil against *E. coli*, *S. aureus*, *P. aeruginosa*, *S. typhi*, and *K. pneumoniae* were determined to be 0.003%, 0.033%, 0.033%, 0.067%, and 0.067%, respectively [30].

The essential oil from the aerial parts of *Z. tenuior* at the flowering stage was obtained using the hydrodistillation process and evaluated via GC and GC-MS. Forty-four components were detected, accounting for 99.8% of the total oil content. The principal components of *Z. tenuior* essential oil were α-terpineol (16.2%), thymol (10.4%), and geranyl acetate (5.2%). The antibacterial efficacy of essential oil was assessed using a micro broth dilution technique. The minimal inhibitory concentration values for saprophytic fungi (*Aspergillus flavus*, *A. parasiticus*, *A. niger*) were lower than those of other microorganisms, and the essential oil had an inhibitory action against the fungi. The antibacterial efficacy of the essential oil was contingent upon the specific pathogen involved. *P. aeruginosa* and *Enterococcus faecalis* exhibited reduced sensitivity to the essential oil, which demonstrated a bactericidal action against *P. aeruginosa*, *E. faecalis*, and *Bacillus cereus* [79].

Ozturk and Ercisli aimed to analyze the chemical composition of essential oil and the *in vitro* antibacterial properties of both essential oil and methanol extracts of *Z. persica*. The inhibitory effects of essential oil and methanol extracts of *Z. persica* were evaluated against 98 isolates from 51 bacterial species using disc-diffusion and micro-broth dilution methods. GC and GC/MS tests indicated that the essential oil primarily comprises (+)-pulegone (79.33%), limonene (6.78%), and piperitenone (4.2%). The antibacterial assay results indicated that both the methanol extract and the essential oil of *Z. persica* exhibited antibacterial activity against several tested bacterial strains. The minimal inhibitory concentration (MIC) values of 7.81 µg/mL were recorded for the essential oil of *Z. persica* against *Bacillus dipsauri*, *Corynebacterium cystitidis*, and *Corynebacterium flavescens*. The MIC value of the methanol extract was 15.60 against *Arthrobacter agilis* [7].

Ma et al. sought to evaluate the *in vitro* and *in vivo* effects of *Z. clinopodioides* essential oil on *Sclerotinia sclerotiorum* in rapeseed plants (*Brassica campestris* L.). GC-MS tests identified 21 chemicals constituting 98.3% of the total extracted oil, predominantly including pulegone (53.5%), isomenthone (10.4%), and carvone (5.7%). The mycelial development of *S. sclerotiorum* was entirely suppressed at essential oil concentrations of 1.25 and 0.15 µL/mL under contact and vapor phase conditions, respectively. During the contact phase, the germination of sclerotia was suppressed at a concentration of 1.00 µL/mL. A vapor phase concentration of essential oil at 0.15 µL/mL had a

significant inhibitory effect on sclerotial germination. The essential oil concentration-dependently reduced the growth of *S. sclerotiorum* on detached rapeseed leaves and potted rapeseed plants. Significant morphological alterations were also noted in the fungal hyphae and sclerotia. Both *in vitro* and *in vivo* findings demonstrated that the essential oil can effectively suppress the growth of *S. sclerotiorum*. According to the results of this study, the essential oil of *Z. clinopodioides* may be utilized for agricultural protection [71].

Their antibacterial efficacies of the methanol and dichloromethane extracts obtained from *Z. tenuior* leaves were evaluated against *S. aureus, E. coli*, methicillin-resistant *S. aureus*, and vancomycin-resistant *Enterococcus* bacterial strains. Furthermore, these extracts exhibited significant antibacterial efficacy against the examined pathogens, particularly *S. aureus* and vancomycin-resistant *Enterococcus* [80].

The antibacterial efficacies of the essential oils of *Z. clinopodioides* and *Z. tenuior* were tested against seven significant foodborne pathogenic microorganisms. The essential oils exhibited a satisfactory antibacterial activity against the examined microorganisms. The maximum inhibitory diameter of *Z. clinopodioides* was recorded for *Bacillus pumilus* (19 ± 0.3 mm) and *Bacillus subtilis* (19 ± 0.4 mm), while the minimum inhibitory diameter was observed for *E. coli* (12 ± 0.3 mm). In contrast, the highest inhibitory diameter of *Z. tenuior* was noted for *B. subtilis* (19 ± 0.3 mm) and *B. cereus* (19 ± 0.1 mm), with the lowest inhibitory diameters recorded for *K. pneumoniae* (13 ± 0.3 mm) and *E. coli* (12 ± 0.4 mm). Consequently, the essential oils demonstrated high bactericidal activities against *B. pumilus, B. subtilis, S. aureus*, and *B. cereus* [73].

5.2. Antioxidant Activity

Gholivand et al. examined the flavonoids, anthocyanins, antioxidant capacity, total phenolic content, ascorbic acid levels, and the essential oil components of *Z. tenuior* in polar and non-polar subfractions at distinct growth phases (pre-flowering and flowering). The antioxidant activities of the materials were assessed using three testing methods: DPPH, *β*-carotene/linoleic acid, and reducing power assay. The non-polar subfraction of the methanol extract exhibited the strongest radical scavenging activity in the DPPH system during the blooming stage (IC_{50} 43.17 ± 3.68 µg/mL). Significant variations in the levels of phenolic compounds, antioxidant activity, anthocyanins, and flavonoids of *Z. tenuior* were observed during two growth phases. The chemical composition of the hydrodistilled essential oil from the aerial parts of *Z. tenuior* was investigated using GC/MS and compared across two growth phases. The primary components of the 28 discovered chemicals in the essential oil were determined to be pulegone (67.34% vs. 59.61%), *β*-humulene (3.24% vs. 3.25%), and limonene (5.06% vs. 2.57%) during the flowering and pre-flowering stages, respectively [81].

Hatami sought to conduct a phytochemical analysis of the methanol and dichloromethane extracts obtained from *Z. tenuior* leaves utilizing GC-MS. The antioxidant activity of the extracts was assessed using the DPPH test. According to the findings, 90-92% of these extracts comprised phytocompounds having therapeutic potential. Among these compounds, pulegone represented the largest proportion of the extracts, accounting for 62% of the methanolic extract and 81% of the dichloromethane extract. Both methanolic and dichloromethane extracts exhibited significant antioxidant activity, with IC_{50} values of 277.6 µg/mL and 49.6 µg/mL, respectively [80].

Konyalıoglu et al. aimed to examine the preventive benefits of essential oils derived from two *Ziziphora* subspecies against H_2O_2-induced oxidative damage in human erythrocytes. The activities of catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), as well as the effects of lipid peroxidation (LPO) and reduced glutathione (GSH) levels of the essential oils on erythrocytes, were evaluated. The findings demonstrated that both essential oils from *Ziziphora* species were efficient on the antioxidant enzyme systems of erythrocytes in comparison to the H_2O_2 group. *Z. taurica* subsp. *taurica* showed a higher effect than the endemic *Z. taurica* subsp. *cleonioides* regarding the CAT, GPx, and SOD enzyme systems in erythrocytes. This study determined that the essential oil of *Z. taurica* subsp. *taurica* comprised caryophyllene oxide (26.16%), *β*-caryophyllene (24.80%), and germacrene-D (7.92%), while *Z. taurica* subsp. *cleonioides* contained (+)-pulegone (69.24%), piperitenone (6.47%), and limonene (3.59%). The results indicated that the essential oils exhibit

antioxidant capabilities, making them suitable for application in the nutraceutical or pharmaceutical sectors [84].

Wu et al. aimed to investigate the protective impact of *Z. clinopodioides* flavonoids (ZCF) against H_2O_2-induced oxidative stress in Human Umbilical Vein Endothelial Cells (HUVEC). The MTT assay was used to assess the viability of HUVEC after pre-treatment with ZCF. Fluorescent microscopy was utilized to assess the apoptosis of HUVEC. Additionally, the impact of ZCF on the activities of the antioxidants SOD, GPx, CAT, malondialdehyde (MDA) generation, and lactic dehydrogenase (LDH) levels was examined. Apoptosis was detected by Hoechst 33258 staining and acridine orange staining. Real-time fluorescence quantitative polymerase chain reaction (Real-time PCR) was employed to assess the mRNA expression levels of B-cell lymphoma/leukemia-2 (Bcl-2), Bcl-2-associated X protein (Bax), and aspartate proteolytic enzyme-3 (Caspase-3). The expression levels of vascular endothelial growth factor receptor 2 (VEGFR2), protein kinase B (Akt), phosphorylated protein kinase B (p-Akt), Bax, Bcl-2, and Caspase-3 were assessed by western blot analysis. ZCF reduced H_2O_2-induced cytotoxicity. Furthermore, ZCF reduced MDA and LDH levels, enhanced SOD, GPx and CAT activity, and prevented apoptosis. Additionally, pre-treatment with ZCF diminished the mRNA expression of Bax and Caspase-3, increased the mRNA expression of Bcl-2, reduced the protein levels of VEGFR2, Bax, and Caspase-3, and enhanced the protein levels of p-Akt/Akt and Bcl-2 in HUVEC cells. The results indicated that ZCF protected against H_2O_2-induced damage in HUVEC cells. The mechanism underlying this impact pertains to the augmentation of antioxidant capacity, inhibition of angiogenesis and induction of apoptosis [72].

Hazrati et al. investigated the chemical composition of essential oils extracted from the aerial blooming parts of *Z. clinopodioides* and *Z. tenuior*, using GC and GC–MS. A total of 17 and 21 compounds (accounting for 99.7% of the total essential oil) were discovered in *Z. clinopodioides* and *Z. tenuior*, respectively. The principal chemicals detected in the essential oil analysis were pulegone (70.4%) and menthone (11.5%) for *Z. clinopodioides*, and pulegone (55.1%) and limonene (8.2%) for *Z. tenuior*. Both *Ziziphora* species exhibited a high concentration of phenolic compounds and demonstrated significant antioxidant properties with IC_{50} values of 147.2 ± 1.3 μg/mL for *Z. tenuior* and 111.4 ± 1.2 μg/mL for *Z. clinopodioides* in DPPH assay. The results demonstrated that the reducing power of *Z. tenuior* was 7.5 ± 1.2 μg/mL, whereas *Z. clinopodioides* exhibited a value of 6.1 ± 0.7 μg/mL [73].

Duque-Soto et al. investigated the potential antioxidant activities of some Lamiaceae species. According to their results, 50% ethanol extract obtained from *Z. hispanica* showed good antioxidant activity with the value of 3.37 μmol Trolox eq./mg dry extract in ORAC test [85].

5.3. Cardiotropic Activity

The objective of the study conducted by Whaley et al. was to evaluate the traditional application of *Z. clinopodioides* subsp. *bungeana* in treating coronary heart problems through *in vivo* models and to identify the active chemicals responsible for its efficacy. Various extracts were prepared from the aerial parts of *Z. clinopodioides* subsp. *bungeana* employing maceration, liquid-liquid extraction, CO_2 extraction, and ultrasound-assisted extraction. The crude extract was progressively subjected to extraction with *n*-hexane and dichloromethane, followed by separation by chromatography on a Diaion HP-20 column. Extracts derived from *Z. clinopodioides* subsp. *bungeana* underwent pharmacological assessment to determine their effectiveness against hemic hypoxia. From the data obtained, two extracts (aqueous residue and ultrasound-assisted extraction by 60% ethanol) were selected for further assessment of their cardiotropic activity. The modeling of chronic heart failure was conducted following these stages: 1) Anesthesia with chloral hydrate at a dosage of 450 mg/kg, administered intraperitoneally, 2) artificial lung ventilation, 3) thoracotomy, 4) induction of permanent ischemia or ischemic-reperfusion injury. Both extracts influenced the indices of contraction and output, close to the reference medicine, monopril. Three novel monoterpenoid derivatives including ziziphoric acid **(58)**, ziziphoroside D **(68)**, and 6′-malonylziziphoroside A **(67)** were identified, alongside two previously documented megastigmane glucosides namely blumenol C glucoside **(82)** and blumenol C 9-*O*-(6′-*O*-malonyl-*β*-D-glucopyranoside) **(83)**, as well as two previously characterized monoterpenoids, 7α-hydroxymintlactone **(59)**, 7-hydroxypiperitone **(60)**, and six

polyphenols including pinocembrine-7-*O*-rutinoside **(45)**, chrysine-7-*O*-rutinoside **(46)**, acacetin-7-*O*-rutinoside **(37)**, luteolin-7-*O*-rutinoside **(43)**, rutin **(57)**, and rosmarinic acid **(12)** were isolated from *Z. clinopodioides* subsp. *bungeana*. These findings corroborate the conventional application of *Z. clinopodioides* subsp. *bungeana* in the management of cardiac ailments [60].

5.4. Immunomodulatory Activity

Protoscolices were treated with six concentrations (3, 5, 10, 25, 50, and 100 mg/mL) of *Z. tenuior* extract and its fractions (ethanol, petroleum ether, ethyl acetate, and chloroform) for 10, 20, 30, 40, 50, and 60 minutes in order to assess the scolicidal and immunomodulatory effect of the extract and its fractions. The viability of the protoscolices was assessed using 1.0% eosin. In order to investigate the immunomodulatory effects of *Ziziphora* and its fractions on macrophage cells, the MTT assay was used to determine the non-toxic concentration of extract and various fractions. The Griess reaction was then used to measure the amount of nitrite, an indicator of nitric oxide, produced by the macrophage cells at 10, 100, and 200 mg/mL over the course of 24 hours at 37°C. All protoscolices were killed in 20 minutes by the *Z. tenuior* extract at a dosage of 10 mg/mL. The scolicidal period was shortened to 10 minutes by raising the concentration to 25 mg/mL. The ethanolic fraction of *Z. tenuior* exhibited the strongest scolicidal activity when compared to the other fractions. The extract showed a decrease in nitric oxide generation and an inhibitory effect on macrophage activity. Even though petroleum ether and ethanolic fractions decreased the formation of nitric oxide, this impact was only noticeable at concentrations of 10 and 100 mg/mL. Although the *Z. tenuior* extract and its fractions were efficient against protoscolices, the whole extract had a significant impact. According to these results, the extract may have anti-inflammatory qualities, as may its ethanolic and petroleum ether fractions [83].

5.5. Anti-inflammatory Activity

Kianpour et al. examined the protective properties of *Z. tenuior* extract against chlorpyrifos (CPF), a widely utilized insecticide in Asia and Africa, focusing on apoptotic and inflammatory pathways in liver and lung tissues of a rat model. The trials were conducted via gavage in male rats over 8 weeks. The extract of *Z. tenuior* was administered at three dosages (40, 80, 160 mg/kg). 6.75 mg/kg CPF was administered as the maximum tolerated dose according to previous studies of the authors. The previous studies showed that CPF can enhance the expression of some inflammatory genes (IL-6, TLR-2, IL-1β, TNF-α, and NLPR3) and apoptosis-related genes (Caspase 3, Caspase 9, Caspase 8, and Bax). Conversely, it can downregulate the expression of the Bcl-2 gene. The post-treatment of *Z. tenuior* extract in CPF-treated rats resulted in a considerable reduction of apoptotic and inflammatory gene expression in the liver and lungs, attributable to its anti-apoptotic properties, as evidenced by the upregulation of the Bcl-2 gene. The current investigation indicated that *Z. tenuior* extract, as a conventional remedy, can mitigate CPF toxicity through a substantial impact on inflammatory and apoptotic cell death signaling pathways. Preliminary studies indicated that *Z. tenuior* extract may mitigate the detrimental effects of CPF on liver and lung tissues [82].

Shabbir et al. aimed to investigate the ability of *Z. clinopodioides* extracts to mitigate joint inflammation utilizing a model of chronic joint inflammation (Freund's complete adjuvant (FCA)-induced rheumatoid arthritis). The research further examines the impact on joint inflammation utilizing acute inflammatory paw edema models. The anti-inflammatory properties were further corroborated by employing the xylene-induced ear edema model. The results suggested that *Z. clinopodioides* effectively improved rheumatoid arthritis, as seen by the reduction of arthritic progression and paw edema. Histopathological analysis revealed a considerable reduction in pannus development, osseous erosion, and synovial inflammation. The administration of plant extracts nearly restored the levels of red blood cells (RBCs), platelets, total leukocytes, and hemoglobin (Hb) content. Biochemical tests (AST, ALT, urea, and creatinine) indicated that plant extracts decreased hepatotoxic or nephrotoxic effects. Water displacement plethysmometry demonstrated that *Z. clinopodioides* greatly reduced carrageenan-induced paw edema. The mechanism was assessed by further evaluating anti-inflammatory properties utilizing histamine- and serotonin-induced paw edema models. *Z. clinopodioides* markedly reduced paw edema induced by histamine and serotonin, and also inhibited

xylene-induced ear edema. This indicated that the suppression of autacoids is one mechanism behind the anti-inflammatory actions of the plant. GC–MS investigation revealed that the plant is abundant in essential oils, comprising terpenoids, esters, alcohols, furans, cyclic ketones, epoxides, oxanes, and acyclic hydrocarbons. In conclusion, the current investigation indicated that *Z. clinopodioides* exhibited strong antiarthritic and anti-inflammatory activities, potentially due to the suppression of autacoids [74].

5.6. Cytotoxic Activity

In a study conducted by Youssif et al., 57 metabolites, including flavonoids, phenolic acids, anthocyanins, and coumarins in the extract of *Z. capitata* aerial parts were determined. Sequential extracts (hexane, chloroform, ethyl acetate, 95% ethanol, and water) were evaluated for *in vitro* cytotoxic activity against HepG-2, MCF-7, HCT-116, A549, and PC3 cell lines. The findings indicated that the hexane extract demonstrated the highest cytotoxic activity against PC3 and A549 cell lines, with IC_{50} values of 47.1 ± 1.75 and 49.2 ± 1.08 μg/mL, respectively. In comparison, vinblastine exhibited IC_{50} values of 42.47 ± 1.95 and 24.64 ± 1.18 μg/mL. Additionally, the hexane extract showed a moderate effect on the other cell lines. The chloroform and ethyl acetate extracts demonstrated moderate affinity across all tested cell lines. Furthermore, the total phenolic and flavonoid contents were evaluated. Molecular docking simulations were conducted at the active sites of VEGFR-2 and TS, identified as anticancer targets for the top ten phytochemicals. The findings indicated that VEGFR-2 exhibited greater binding energy values than human thymidylate synthase when compared to vinblastine and co-crystallized ligands [86].

5.7. Vasorelaxant Activity

Senejoux et al. (2010) examined the vasodilatory effects of *Z. clinopodioides* and investigated the mechanisms involved, providing a pharmacological basis for its traditional use. The effects of hexane, dichloromethane, and aqueous extracts of *Z. clinopodioides* were assessed on isolated rat aortic rings that were pre-contracted with phenylephrine (PE) or high KCl. The mechanisms were assessed using *Z. clinopodioides* dichlorometane extract, the most effective extract. This extract caused relaxation in endothelium-intact aortic rings that were pre-contracted with phenylephrine (PE, 10^{-6} M) or high KCl (6×10^{-2} M), yielding EC_{50} values of 0.27±0.03 and 0.34±0.04 g/L, respectively. The mechanical removal of the endothelium did not significantly alter the relaxation induced by *Z. clinopodioides* dichlorometane extract. The vasorelaxant effect of *Z. clinopodioides* dichlorometane extract in endothelium-denuded aorta pre-contracted with PE (10^{-6} M) was significantly diminished by 4-amino-pyridine (10^{-3} M), while glibenclamide (10^{-4} M), iberiotoxin (3×10^{-8} M), and thapsigargin (10^{-7} M) did not exert a significant effect. *Z. clinopodioides* dichlorometane extract significantly inhibited extracellular Ca^{2+}-induced contraction in high KCl and PE pre-contracted rings in a Ca^{2+}-free solution. Furthermore, *Z. clinopodioides* dichlorometane extract inhibited the intracellular Ca^{2+} release that is sensitive to PE (10^{-6} M). The findings indicated that *Z. clinopodioides* dichlorometane extract displays endothelium-independent vasodilatory effects, which are facilitated by the inhibition of extracellular Ca^{2+} influx via voltage- and receptor-operated Ca^{2+} channels (VDDCs and ROCCs), the suppression of Ca^{2+} release from intracellular stores, and the activation of voltage-dependent K+ channels [75].

Senejoux et al. (2012) used an *in vitro* model of rat isolated thoracic aortic rings to undertake an activity-guided fractionation of a hydroalcoholic extract of the plant in order to identify and assess the bioactive components. The following seven substances were shown to be active principles: ethyl 4-coumarate, acacetin, apigenin, chrysin, thymonin, acetovanillone, and 4-hydroxyacetophenone. The most effecitve ones were ethyl 4-coumarate, chrysin, and apigenin. The findings offer the first proof that phenolic components mediate, at least partially, the vasodilation caused by *Z. clinopodioides* [59].

5.8. Anti-atherosclerotic Activity

Wu et al. aimed to examine the *in vivo* anti-atherosclerosis effects and mechanisms of *Z. clinopodioides* flavonoids (ZCF). Network pharmacology technology was employed to anticipate and

study the primary chemical constituents, action targets, and signaling pathways of *Z. clinopodioides*. The primary bioactive constituents of *Z. clinopodioides* were characterized by LC-MS. *In vivo* tests involved inducing atherosclerosis in rats using a high-fat emulsion mixed with vitamin D_3, followed by treatment with simvastatin (0.45 mg/kg/d) and ZCF (6.25, 12.5, 25 g/kg/d) over 7 weeks. ZCF markedly diminished blood lipid levels (TG, TC, and LDL-C), reduced lipid accumulation in the aorta and the extent of atherosclerotic lesions, and blocked the impairment of mitochondrial membrane potential (MMP2/9/12/13). Concurrently, ZCF may attenuate the levels of VEGF, AKT, NF-κB, ICAM-1, and VCAM-1 proteins, suggesting that ZCF may exert an anti-atherosclerotic effect by inhibiting the VEGF/AKT/NF-κB signaling pathway. The findings of this study indicated that ZCF displays an anti-atherosclerotic activity to reduce cholesterol levels and safeguard endothelial function, exhibiting antioxidant and anti-inflammatory properties, suggesting that ZCF may serve as a viable therapeutic agent in the prevention of atherosclerosis [76].

5.9. Insecticidal Activity

Bunium persicum (Boiss.) B Fedtsch. and *Z. clinopodioides* are two economically significant fragrant plants recognized for their traditional culinary and medicinal applications. Their essential oils exerted notably significant insecticidal efficacy against diverse targets. The phytochemical analysis of the two essential oils indicated a predominance of γ-terpinene (35.8%), cumin aldehyde (16.6%), γ-terpinen-7-al (14.0%), and α-terpinen-7-al (11.7%) in *B. persicum*, whereas *Z. clinopodioides* exhibited predominance of pulegone (55.6%), piperitenone (12.8%), and isomenthone (8.0%). Nanoemulsions were successfully produced using high-pressure homogenization or ultrasonication, utilizing polysorbate 80 as the emulsifying agent. The essential oils and their 10% nanoemulsion (NE)s were assessed against the larvae and pupae of *Culex quinquefasciatus* Say mosquitoes. Both essential oils demonstrated significant larvicidal effectiveness, with LC_{50} values of 35.8 μL/L for *B. persicum* and 68.9 μL/L for *Z. clinopodioides*. The NE of essential oil of *B. persicum* demonstrated higher efficacy than the essential oil alone (LC_{50} = 290.4 μL/L), given that only 10% of the essential oil was encapsulated. In contrast, *Z. clinopodioides* nanoemulsion exhibited equivalent efficacy to the essential oil (LC_{50} of 759.8 μL/L). Furthermore, both NEs exhibited markedly superior sublethal toxicity in comparison to the essential oils. Furthermore, despite the absence of notable mortality during the pupal stage, merely 12% of the larvae underwent pupation and emerged as adults in the case of the NE from *B. persicum*. In conclusion, both essential oils and nanoemulsions may serve as viable candidates for the formulation of botanical pesticides, taking into account their commercial availability and cost-effectiveness [77].

5.10. Neuroprotective Activity

A recent study has emphasized neuroprotective properties of *Z. clinopodioides*. In conditions affecting the central nervous system, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and cerebral ischemia-reperfusion injury, flavonoid-rich preparations of *Z. clinopodioides* have shown to be promising. About 25 flavonoids, including linarin, acacetin, hyperoside, quercetin, apigenin, luteolin, chrysin, kaempferol, baicalein, and rutin, have been identified from different plant parts. Through mechanisms including autophagy regulation, antioxidant, anti-inflammatory, anti-apoptosis, and endoplasmic reticulum stress responses, these drugs demonstrate neuroprotective effects both *in vitro* and *in vivo*. Research on the extracts and their processes in neurological illnesses is still scarce, despite encouraging results. The work highlights the necessity of additional research on these flavonoids' biosynthesis pathways and chemical changes to completely investigate and improve their neuroprotective potential and establish a basis for therapeutic applications [78].

6. Conclusions

The Lamiaceae family has a wide variety of fragrant and medicinal plant species, one such is the genus *Ziziphora*. The high percentage of pulegone in the essential oil of this genus gives it a distinct flavor and perfume, which is why it's used as a spice and tea for pleasure as well as for medicinal

purposes. This review provided details on the phytochemicals, bioactivities, and ethnobotanical applications of *Ziziphora* species. *Ziziphora* species have long been utilized in traditional folk medicine in many countries to treat serious illnesses. Indeed, these plants' medicinal properties have been documented for ages in the treatment of colds, fevers, inflammation, digestive disorders, sleeplessness, bleeding, and cardiovascular malfunctions. Aqueous extracts, tinctures, decoctions, and infusions are frequently employed. Their potential as cytotoxic, antibacterial, antioxidant, antifungal, and immunostimulatory drugs has been revealed by biological activity studies. Numerous studies have examined the antibacterial and antifungal properties of *Ziziphora* plants against a wide range of microorganisms, including fungi and bacteria. Furthermore, some investigations have reported strong antioxidant properties of *Ziziphora* species for both essential oil and extracts. The phytochemicals found in *Ziziphora*, which are a classic representative of the Lamiaceae family, are particularly represented by triterpenes, phenolic compounds consists the flavonoids and phenolic acids, and essential oil. These specific compounds' confirmed activity can be interpreted as evidence of their traditional uses, documented biological activities, and support for a large number of patent applications. The best well-established species in this genus, *Z. clinopodioides*, is responsible for the highest rates of scientific recordings in *Ziziphora* species. Several phytochemical findings have also been published on *Z. tenuior* L., another member in this genus. Given the overall effectiveness and therapeutic effects of these chemicals, as well as the fact that they are abundant in many *Ziziphora* species extracts, it will be beneficial to create novel herbal-based natural medications based on these plants in the near future.

ORCID
Mert Ilhan: 0000-0001-5042-3915
Perihan Gürbüz: 0000-0002-3056-411X
İpek Süntar: 0000-0003-4201-1325

References

[1] M.H.K. Abad and M. Nadaf (2022). The ethnobotanical properties and medicinal application of essential oils of *Ziziphora persica* Bunge from different habitats: A review, *J. Essent. Oil Res.* **35,** 177-196.
[2] F. Satıl and S. Selvi (2020). Ethnobotanical features of *Ziziphora* L. (Lamiaceae) taxa in Turkey, *Int. J. Nat. Life Sci.* **4,** 56-65.
[3] F. Naghibi, M. Mosaddegh, S.M. Mohammadi and A. Ghorbani (2005). Labiatae family in folk medicine in Iran: From ethnobotany to pharmacology *Iran. J. Pharm. Res.* **4,** 63-79.
[4] M.T. Babac (2004). Possibility of an information system on plants of South-West Asia with particular reference to the Turkish Plants Data Service (TÜBİVES) *Turk. J. Bot.* **28,** 119-127.
[5] S. Selvi, F. Satil, E. Martin, S. Celenk and T. Dirmenci (2015). Some evidence for infrageneric classification in *Ziziphora* L. (Lamiaceae:Mentheae), *Plant Biosyst.* **149,** 415-423.
[6] K. Smejkal, M. Malanik, K. Zhaparkulova, Z. Sakipova, L. Ibragimova, G. Ibadullaeva and M. Zemlicka (2016). Kazakh *Ziziphora* species as sources of bioactive substances, *Molecules* **21,** 826.
[7] S. Ozturk and S. Ercisli (2006). The chemical composition of essential oil and *in vitro* antibacterial activities of essential oil and methanol extract of *Ziziphora persica* Bunge, *J. Ethnopharmacol.* **106,** 372-376.
[8] A. Kaya, F. Satil, T. Dirmenci and S. Selvi (2013). Trichome micromorphology in Turkish species of *Ziziphora* (Lamiaceae), *Nord. J. Bot.* **31,** 270-277.
[9] E. Sezik and G. Tümen (1990). Constituents of the essential oil of *Ziziphora taurica* subsp. *cleonioides* (Boiss.) Davis growing in Turkey, *J. Islam. Acad. Sci.* **3,** 113-117.
[10] K.H.C. Baser, E. Sezik and G. Tümen (1991). Composition of the essential oil of *Ziziphora clinopodioides* Lam, *J. Essent. Oil Res.* **3,** 237-239.
[11] A. Nezhadali and B.Z. Shirvan (2010). Separation, identification and determination of volatile compounds of *Ziziphora persica* Bunge using HS-SPME/GC-MS, *Int. J. Environ. Sci. Dev.* 115-118.
[12] IPNI (2025). International Plant Names Index. Published on the Internet http://www.ipni.org, The Royal Botanic Gardens, Kew, Harvard University Herbaria & Libraries and Australian National Herbarium. [Retrieved 12 May 2025].

[13] POWO (2025). "Plants of the World Online. Facilitated by the Royal Botanic Gardens, Kew. Published on the Internet; https://powo.science.kew.org/ Retrieved 15 May 2025.",
[14] E. Sezik and G. Tümen (1988). Türkiye'de halk İlacı ve çay olarak kullanılan bitkiler üzerinde morfolojik ve anatomik araştırmalar VI. *Ziziphora taurica* Bieb. subsp. *cleonioides* (Boiss.) Davis, *Uludağ Üniv. Eğitim Fak. Derg. III* **3,** 65-73.
[15] S. Ozturk and S. Ercisli (2007). Antibacterial activity and chemical constitutions of *Ziziphora clinopodioides*, *Food Control* **18,** 535-540.
[16] E. Sezik and G. Tümen (1989). *Ziziphora capitata* L. üzerinde morfolojik ve anatomik araştırmalar, *Uludağ Üniv. Eğitim Fak. Derg.* **4,** 13-20.
[17] F. Koca, S. Erken, G. Tümen and K.H.C. Başer (1995). *Ziziphora clinopodioides* Lam. üzerinde morfolojik ve anatomik araştırmalar, *Turk. J. Bot.* **19,** 135-144.
[18] A. Zargari (1995). Iranian medicinal plants, Tehran University press, Tehran.
[19] Z. Aghajani, F. Assadian, S. Masoudi, F. Chalabian, A. Esmaeili, M. Tabatabaei-Anaraki and A. Rustaiyan (2008). Chemical composition and *in vitro* antibacterial activities of the oil of *Ziziphora clinopodioides* and *Z. capitata* subsp. *capitata* from Iran, *Chem. Nat. Compd.* **44,** 387-389.
[20] M. Beikmohammadi (2011). The evaluation of medicinal properties of *Ziziphora clinopodioides*, *World Appl. Sci. J.* **12,** 1635-1638.
[21] Y. Öztürk, S. Aydm, B. Tecik and K.H.C. Başer (1995). Effects of essential oils from certain *Ziziphora* species on swimming performance in mice, *Phytother. Res.* **9,** 225-227.
[22] E. Sezik, E. Yesilada, H. Shadidoyatov, Z. Kulivey, A.M. Nigmatullaev, H.N. Aripov, Y. Takaishi, Y. Takeda and G. Honda (2004). Folk medicine in Uzbekistan. I. Toshkent, Djizzax, and Samarqand provinces, *J. Ethnopharmacol.* **92,** 197-207.
[23] E. Özdemir (2005). Niğde-Aladağlar'ın batısında etnobotanik bir araştırma, Publisher, İstanbul.
[24] S. Mart (2006). Bahçe ve Hasanbeyli (Osmaniye) halkının kullandığı doğal bitkilerin etnobotanik yönden araştırılması, Publisher, Adana.
[25] O. Koyuncu, Ö.K. Yaylacı, D. Öztürk, E. Potoğlu, İ., F. Savaroğlu, Ö. Akçoskun and M. Ardıç (2010). Risk categories and ethnobotanical features of the Lamiaceae taxa growing naturally in Osmaneli (Bilecik/Turkey) and environs, *Biol. Diversity Conservation* **3,** 31-45.
[26] S. Demirci and N. Özhatay (2012). An ethnobotanical study in Kahramanmaraş (Turkey); Wild plants used for medicinal purpose in Andırın, Kahramanmaraş, *Turk. J. Pharm. Sci.* **9,** 75-92.
[27] A. Doğan (2015). Wild edible plants of Pertek (Tunceli-Turkey), *Marmara Pharm. J.* **2,** 126-126.
[28] F. Abak (2018). Şanlıurfa ili Lamiaceae (Ballıbabagiller) familyasının florası bazı taksonların fitokimyasal ve etnobotanik özellikleri, Publisher, Rize.
[29] T. Baytop (1999). Türkiye'de Bitkiler ile Tedavi. , İstanbul Üniversitesi Yayınları, İstanbul.
[30] J. Behravan, M. Ramezani, M.K. Hassanzadeh, M. Eskandari, J. Kasaian and Z. Sabeti (2007). Composition, antimycotic and antibacterial activity of *Ziziphora clinopodioides* Lam. essential oil from Iran, *J. Essent. Oil-Bear. Plants* **10,** 339-345.
[31] E. Altundağ (2009). Iğdır ilinin (Doğu Anadolu Bölgesi) doğal bitkilerinin halk tarafından kullanımı, Publisher, Istanbul.
[32] M. Ahvazi, F. Khalighi-Sigaroodi, M.M. Charkhchiyan, F. Mojab, V.A. Mozaffarian and H. Zakeri (2012). Introduction of medicinal plants species with the most traditional usage in Alamut region, *Iran. J. Pharm. Res.* **11,** 185-194.
[33] M. Furukawa, N. Oikawa, T. Imohata, M. Makino, S. Ogawa, T. Iida, Y. Fujimoto and S. Kitanaka (2012). Monoterpene glucosides from *Ziziphora clinopodioides* (Labiatae), *Chem. Pharm. Bull. (Tokyo)* **60,** 397-401.
[34] Y. Ye, Bahang, Y. Liu, G. Zou and H.A. Aisa (2012). Chemical constituents of *Ziziphora clinopodioides*, *Chem. Nat. Compd.* **48,** 681-682.
[35] Ş. Alp, H. Doğan, E. Temim, A. Leto, M. Zia-Ul-Haq, A. Hadziabulic and H. Aladag (2016). Chemical composition and antioxidant activity *Ziziphora clinopodioides* ecotypes from Turkey, *Rom. Biotechnol. Lett.* **21,** 11298-11303.
[36] Q. Meng, G. Li, B. Luo, L. Wang, Y. Lu and W. Liu (2016). Screening and isolation of natural antioxidants from *Ziziphora clinopodioides* Lam. with high performance liquid chromatography coupled to a post-column Ce(iv) reduction capacity assay, *RSC Advances* **6,** 62378-62384.
[37] Y. Shahbazi and N. Shavisi (2016). Interactions of *Ziziphora clinopodioides* and *Mentha spicata* essential oils with chitosan and ciprofloxacin against common food-related pathogens, *LWT - Food Sci. Technol.* **71,** 364-369.

[38] M. Mohammadhosseini (2017). The ethnobotanical, phytochemical and pharmacological properties and medicinal applications of essential oils and extracts of different *Ziziphora* species, *Ind. Crops Prod.* **105,** 164-192.
[39] S. Sancaktaroğlu (2017). *Ziziphora persica* Bunge ve *Thymus vulgaris* L. türlerinin *in vitro* rejenerasyonu üzerine farklı eksplant tiplerinin ve bitki büyüme düzenleyicilerinin etkisi, Publisher, Iğdır.
[40] M. Pardo de Santayana, E. Blanco and R. Morales (2005). Plants known as te in Spain: An ethno-pharmaco-botanical review, *J. Ethnopharmacol.* **98,** 1-19.
[41] D.N. Olennikov and A.A. Akobirshoeva (2016). Flavonoids and phenylpropanoids of *Nepeta glutinosa* and *Ziziphora pamiroalaica*, *Chem. Nat. Compd.* **52,** 909-912.
[42] L. Pawera, V. Verner, C. Termote, I. Sodombekov, A. Kandakov, N. Karabaev, M. Skalicky and Z. Polesny (2016). Medical ethnobotany of herbal practitioners in the Turkestan Range, southwestern Kyrgyzstan, *Acta Soc. Bot. Pol.* **85,** 3483.
[43] S.D. Gusakova and T.V. Khomova (1997). Lipids of *Ziziphora pedicellata*, *Chem. Nat. Compd.* **33,** 633-635.
[44] P. Faryadyan, A. Khosravi, S. Faryadian, M. Kashiri and R. Valizadeh (2014). The aqueous extract of *Ziziphora persica* cause positive mood on depressive rat, *Biomed. Pharmacol. J.* **7,** 121-124.
[45] F. Khajoei Nasab and A.R. Khosravi (2014). Ethnobotanical study of medicinal plants of Sirjan in Kerman Province, Iran, *J. Ethnopharmacol.* **154,** 190-197.
[46] Ahvazi M. and M. Akbarzadeh (2017). Traditional uses of some medicinal plants in gastrointestinal tract treatment in east - Mazandaran (Iran), *J. Med. Plants* **16,** 43-56.
[47] H. Akan, M. Aydoğdu, M.M. Korkut and M.M. Balos (2013). An ethnobotanical research of the Kalecik Mountain area (Şanlıurfa, South-East Anatolia), *Biol. Diversity Conservation* **6** 84-90.
[48] N. Ghassemi, M. Ghanadian, L. Ghaemmaghami and H. Kiani (2013). Development of a validated HPLC/Photodiode array method for the determination of isomenthone in the aerial parts of *Ziziphora tenuior* L, *Jundishapur J. Nat. Pharm. Prod.* **8,** 180-186.
[49] I. Karimi, H. Hayatgheybi, S. Motamedi, D. Naseri, T. Shamspur, D. Afzali and A.H. Aghdam (2013). Chemical composition and hypolipidemic effects of an aromatic water of *Ziziphora tenuior* L. in cholesterol-fed rabbits, *J. Appl. Biol. Sci.* **7,** 61-67.
[50] A. Azadmehr, R. Latifi, S. Mosalla, R. Hajiaghaee and M. Shahnazi (2014). Immunomodulatory effects of *Ziziphora tenuior* L. extract on the dendritic cells, *DARU J. Pharm. Sci.* **22,** 63.
[51] M.R. Delnavazi, F. Baba-Ali, S. Soufiabadi, M. Sherafatmand, F. Ghahremani, S. Tavakoli and N. Yassa (2014). Essential oil composition, antioxidant activity and total phenolic content of some Lamiaceae taxa growing in Northwest of Iran, *Pharm. Sci.* **20,** 22-28.
[52] İ. Şenkardeş (2014). Nevşehir' in güney ilçelerinde (Acıgöl, Derinkuyu, Gülşehir, Nevşehir-Merkez, Ürgüp) etnobotanik araştırmalar, Publisher, İstanbul.
[53] M. Bahmani, K. Saki, S. Shahsavari, M. Rafieian-Kopaei, R. Sepahvand and A. Adineh (2015). Identification of medicinal plants effective in infectious diseases in Urmia, northwest of Iran, *Asian Pac. J. Trop. Biomed.* **5,** 858-864.
[54] G. Tümen (1980). *Ziziphora taurica* M. Bieb. subsp. *taurica* J.R. Edmondson üzerinde farmakognozik araştırmalar, Publisher, Ankara.
[55] R. Polat (2010). Havran ve Burhaniye (Balıkesir) çevresinde tarımsal biyoçeşitlilik ve etnobotanik araştırmaları, Publisher, Balıkesir.
[56] Z. Mazarei (2023). Chemical composition and biological activity of *Ziziphora clinopodioides* essential oil: A review, *Jundishapur J. Nat. Pharm. Prod.* **18,** 137776.
[57] N.Z. Mamadalieva, D.K. Akramov, E. Ovidi, A. Tiezzi, L. Nahar, S.S. Azimova and S.D. Sarker (2017). Aromatic medicinal plants of the Lamiaceae family from Uzbekistan: Ethnopharmacology, essential oils composition, and biological activities, *Medicines* **4,** 8.
[58] K.H.C. Baser, K. N. and G. and Tümen (1998). Pulegone-rich essential oils of Turkey, *J. Essent. Oil Res.* **10,** 1-8.
[59] F. Senejoux, C. Demougeot, P. Kerram, H.A. Aisa, A. Berthelot, F. Bevalot and C. Girard-Thernier (2012). Bioassay-guided isolation of vasorelaxant compounds from *Ziziphora clinopodioides* Lam. (Lamiaceae), *Fitoterapia* **83,** 377-382.
[60] A.O. Whaley, D.Y. Ivkin, K.A. Zhaparkulova, I.N. Olusheva, E.B. Serebryakov, S.N. Smirnov, E.D. Semivelichenko, A.Y. Grishina, A.A. Karpov, E.I. Eletckaya, K.K. Kozhanova, L.N. Ibragimova, K.T. Tastambek, A.M. Seitaliyeva, Terninko, II, Z.B. Sakipova, A.N. Shikov, M.N. Povydysh and A.K. Whaley (2023). Chemical composition and cardiotropic activity of *Ziziphora clinopodioides* subsp. *bungeana* (Juz.) Rech.f, *J. Ethnopharmacol.* **315,** 116660.
[61] G. Zou, D. Guo, H. Zhao and H. Aisa (2015). Bioactive constituents of *Ziziphora clinopodioides*, *Chem. Nat. Compd.* **51,** 961-963.

[62] Y. Ye, Bahang, Y. Liu, G. Zou and H.A. Aisa (2012). Chemical constituents of *Ziziphora clinopodioides*, *Chem. Nat. Compd.* **48,** 681-682.

[63] X.-M. Zhang, D.-Q. An, L.-L. Guo, N.-H. Yang and H. Zhang (2019). Identification and screening of active components from *Ziziphora clinopodioides* Lam. in regulating autophagy, *Nat. Prod. Res.* **33,** 2549-2553.

[64] J. He, W. Yang, B. Cheng, L. Ma, D. Tursunjiang, Z. Ding, Y. Li, Z. Wang, Y. Ma and G. Li (2020). Integrated metabolomic and transcriptomic profiling reveals the tissue-specific flavonoid compositions and their biosynthesis pathways in *Ziziphora bungeana*, *Chin. Med.* **15,** 1-15.

[65] R. Mehmood, M. Imran, A. Malik and R.B. Tareen (2010). Ziziphorins A and B. New flavonoids from *Ziziphora tenuior*, *Z. fur Naturforsch. - B* **65,** 1397-1400.

[66] S. Tian, Q. Yu, D. Wang and H. Upur (2012). Development of a rapid resolution liquid chromatography-diode array detector method for the determination of three compounds in *Ziziphora clinopodioides* Lam from different origins of Xinjiang, *Pharmacogn. Mag.* **8,** 280.

[67] J. Zhang, X. Yan, S. Xu, D. Wang and H. Liu (2021). High-performance thin-layer chromatographic quantification of four active compounds in total flavonoids of *Ziziphora clinopodioides* Lam. and TLC–DPPH test for screening antioxidant components, *JPC-J. Planar Chromat.* **34,** 481-492.

[68] D. Olennikov and A. Akobirshoeva (2016). Flavonoids and phenylpropanoids of Nepeta glutinosa and Ziziphora pamiroalaica, *Chem. Nat. Compd.* **52,** 909-912.

[69] M. Malanik, J. Treml, R. Kubínová, G. Vávrová, M. Oravec, J. Marek, K. Zhaparkulova, L. Ibragimova, T. Bekezhanova and A. Karaubayeva (2025). Isolation of a unique monoterpene diperoxy dimer from *Ziziphora clinopodioides* subsp. *bungeana* together with triterpenes with antidiabetic properties, *Phytochem. Anal.* in press.

[70] R. Srivedavyasasri, K. Zhaparkulova, Z. Sakipova, L. Ibragimova and S.A. Ross (2018). Phytochemical and biological studies on *Ziziphora bungeana*, *Chem. Nat. Compd.* **54,** 195-197.

[71] B.X. Ma, X.Q. Ban, J.S. He, B. Huang, H. Zeng, J. Tian, Y.X. Chen and Y.W. Wang (2016). Antifungal activity of *Ziziphora clinopodioides* Lam. essential oil against *Sclerotinia sclerotiorum* on rapeseed plants (*Brassica campestris* L.), *Crop Protect.* **89,** 289-295.

[72] Y. Wu, Y. Wang and X. Nabi (2019). Protective effect of *Ziziphora clinopodioides* flavonoids against H_2O_2-induced oxidative stress in HUVEC cells, *Biomed. Pharmacother.* **117,** 109156.

[73] S. Hazrati, M. Govahi, M. Sedaghat and A. Beyraghdar Kashkooli (2020). A comparative study of essential oil profile, antibacterial and antioxidant activities of two cultivated *Ziziphora* species (*Z. clinopodioides* and *Z. tenuior*), *Ind. Crops Prod.* **157,** 112942.

[74] A. Shabbir, S.A. Batool, M.I. Basheer, M. Shahzad, K. Sultana, R.B. Tareen, J. Iqbal and H. Saeed Ul (2018). *Ziziphora clinopodioides* ameliorated rheumatoid arthritis and inflammatory paw edema in different models of acute and chronic inflammation, *Biomed. Pharmacother.* **97,** 1710-1721.

[75] F. Senejoux, C. Girard, P. Kerram, H.A. Aisa, A. Berthelot, F. Bevalot and C. Demougeot (2010). Mechanisms of vasorelaxation induced by *Ziziphora clinopodioides* Lam. (Lamiaceae) extract in rat thoracic aorta, *J. Ethnopharmacol.* **132,** 268-273.

[76] Y. Wu, Y. Wang, X. Liu, L. Jiang, A. Guli, J. Sailike, X. Sun, N. Abuduwaili, H. Tuoliuhan, K. Maney and X. Nabi (2020). *Ziziphora clinopodioides* flavonoids based on network pharmacology attenuates atherosclerosis in rats induced by high-fat emulsion combined with vitamin D_3 by down-regulating VEGF/AKT/NF-kappaB signaling pathway, *Biomed. Pharmacother.* **129,** 110399.

[77] D.R. Perinelli, R. Pavela, G. Bonacucina, C. Baldassarri, E. Spinozzi, J. Torresi, R. Petrelli, M.R. Morshedloo, F. Maggi, G. Benelli and A. Canale (2022). Development, characterization, insecticidal and sublethal effects of *Bunium persicum* and *Ziziphora clinopodioides*-based essential oil nanoemulsions on *Culex quinquefasciatus*, *Ind. Crops Prod.* **186,** 115249.

[78] L. Gu, C. Wang, J. Liu, M. Zheng, Y. Tan, Q. Du, Q. Li, W. Yang and X. Zhang (2025). Unlocking the neuroprotective potential of *Ziziphora clinopodioides* flavonoids in combating neurodegenerative diseases and other brain injuries, *Biomed. Pharmacother.* **182,** 117744.

[79] M. Mahboubi, N. Kazempour and H. Hosseini (2012). Chemical composition, antimicrobial activity of essential oil from *Ziziphora tenuir* L. aerial parts, *J. Essent. Oil-Bear. Plants* **15,** 545-549.

[80] A. Hatami (2024). Phytochemical characterisation of dichloromethane and methanolic extracts of the *Ziziphora tenuior* leaves and evaluation of their antioxidant and antibacterial activities, *Nat. Prod. Res.* 1-8.

[81] M.B. Gholivand, M. Piryaei and S.M. Maassoumi (2014). Antioxidant activity of *Ziziphora tenuoir* methanolic extracts and comparison of the essential oil in two stages of growth, *Chin. J. Nat. Med.* **12,** 505-511.

[82] F. Kianpour, M. Mohseni, M. Beigmohamadi, A. Yazdinezhad, A. Ramazani, M.J. Hosseini and A. Sharafi (2021). The protective effects of *Ziziphora tenuior* L. against chlorpyrifos induced toxicity: Involvement of inflammatory and cell death signaling pathway, *J. Ethnopharmacol.* **272,** 113959.

[83] M. Shahnazi, A. Azadmehr, A. Andalibian, R. Hajiaghaee, M. Saraei and M. Alipour (2016). Protoscolicidal and immunomodulatory activity of *Ziziphora tenuior* extract and its fractions, *Asian Pac. J. Trop. Med.* **9,** 1062-1068.

[84] S. Konyalıoglu, B. Ozturk and G.E. Meral (2008). Comparison of chemical compositions and antioxidant activities of the essential oils of two *Ziziphora*. Taxa from Anatolia, *Pharm. Biol.* **44,** 121-126.

[85] C. Duque-Soto, I. Borras-Linares, R. Quirantes-Pine, I. Falco, G. Sanchez, A. Segura-Carretero and J. Lozano-Sanchez (2022). Potential antioxidant and antiviral activities of hydroethanolic extracts of selected Lamiaceae species, *Foods* **11,** 1862.

[86] Y.M. Youssif, G.A.M. Elhagali, M.A. Zahran, F.A. Ahmed and A. Ragab (2024). Utilising UPLC-QTOF-MS/MS to determine the phytochemical profile and *in vitro* cytotoxic potential of *Ziziphora capitata* L. with molecular docking simulation, *Nat. Prod. Res.* 1-9.