



## Review: Antioxidant Potential of *Ziziphora Clinopodioides* Lam: A Narrative Review

Mohammad Hossein Hosseinzadeh

Student Research Committee and Pharmaceutical Sciences Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran.

Mohammad Ali Ebrahimzadeh

Student Research Committee and Pharmaceutical Sciences Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran.

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#### Correspondence:

Mohammad Ali Ebrahimzadeh,  
Student Research Committee and  
Pharmaceutical Sciences Research  
Center, Hemoglobinopathy Institute,  
Mazandaran University of Medical  
Sciences, Sari, Iran.

**Email:** zadeh20@yahoo.com

**ORCID:** 0000-0002-8769-9912

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### ABSTRACT

Reactive oxygen species (ROS) are generated by many redox processes that normally occur in the metabolism of aerobic cells. They are highly reactive and harmful to normal cells. If not eliminated, they can damage important molecules, such as DNA and proteins. These harmful effects of free radicals can be blocked by antioxidants, which scavenge the free radicals and detoxify the organism. Plants and plant-derived products contain a wide range of phytochemicals, such as antioxidants, which are thought to have a protective role against the risk of oxidative stress-related diseases. Oxidative stress is an important contributor to the pathophysiology of a variety of pathological conditions such as arteriosclerosis, cancer, gastrointestinal tract disorders, rheumatism, diabetes mellitus, cardiovascular diseases, nephritis, neurodegenerative disease, and inflammatory injury. Recently, interest has considerably increased in finding naturally occurring antioxidants to replace synthetic antioxidants, which were restricted due to their adverse reactions such as carcinogenesis. Natural products have been the basis to treat some human diseases. There is emerging interest in the use of naturally occurring antioxidants for the management of a number of these pathophysiological conditions. Among the various natural sources, endemic medicinal plant species are of particular interest because they may be used for producing raw materials or preparations containing phytochemicals with significant antioxidant capacities and possible health benefits. *Ziziphora Clinopodioides*, known as *Kakuti-e kuhi*, *Ankh*, *Lip vanilla*, and mountain mint, is a wild flowering plant of Lamiaceae family. It is native to the parts of Iran and Iraq. In traditional medicine of Iran, this plant has been used to treat stomach and gastrointestinal pain, inflammatory, and cardiovascular disease, asthma, cough, bronchitis, insomnia, colds, flu, and other infectious diseases. In this paper, published antioxidant activities of *Z. Clinopodioides* were reviewed.

## Introduction

Different abiotic stresses cause the overproduction of reactive oxygen species (ROS). ROS contributes to increased lipid peroxidation, enhanced urinary lipid metabolite excretion, intracellular oxidized state regulation, DNA

and cell membrane disruption, and altered gene expression that leads to numerous medical disorders, such as aging, hypertension, asthma, infectious diseases, carcinogenesis, coronary dysfunction, cataracts, diabetes, neurodegenerative

illnesses, Alzheimer's disease, Parkinson's dementia, etc. (1, 2). Antioxidants neutralize the ROS damage and thus help to prevent diseases. Antioxidants can be synthetic or natural. Research shows synthetic antioxidants are dangerous to humans, so in recent years the search for non-toxic antioxidants has been intensified. Today, the use of natural antioxidants (Plants are one of the rich sources of natural antioxidants) is preferred to synthetic antioxidants due to their low price, dietary compatibility, and harmlessness to the human body (2).

*Ziziphora Clinopodioides*, also known as Kakuti-e kuhi, Ankh, Lip vanilla, and mountain mint, is a wild flowering plant of Lamiaceae family. *Z. Clinopodioides* is native to the parts of Iran, Iraq, Afghanistan, and Talesh (3, 4). This plant contains compounds such as flavonoids, terpenoids, and alkaloids. The plant's flavonoids appear to increase antioxidant properties by inhibiting lipid peroxidation. In traditional medicine of Iran and other Middle East countries, this plant has been used to treat stomach and gastrointestinal pain, inflammatory, and cardiovascular disease, asthma, cough, bronchitis, insomnia, colds, flu, and other infectious diseases (5-7).

There are various methods for evaluating and identifying antioxidants at the *in vitro* level (general free radical scavenging, superoxide anion scavenging, hydroxyl radical scavenging, etc.) that are commonly used and can be supported by the results obtained from *ex vivo* (peroxynitrite scavenging, singlet oxygen scavenging, etc.) and *in vivo* methods (lipid peroxidation, nitric oxide scavenging-bioassay) (8). Therefore, in this paper, we summarize the antioxidant effects reported from *Z. Clinopodioides*.

## Antioxidant activities

Alp et al. showed good antioxidant effects of 8 ecotypes of essential oil of *Ziziphora Clinopodioides* collected from northeast Turkey in the DPPH test. Evaluation of the total phenolic content of these plants showed a direct relationship between this factor and

the antioxidant effects of plants. The strongest ecotype had antioxidant effects with an IC<sub>50</sub> of  $3.60 \pm 0.1$  mg/ml, and total phenolic content of  $55.71 \pm 3.1$  mg gallic acid / 100 g Fresh weight and the weakest ecotype had antioxidant effects with an IC<sub>50</sub> of  $4.20 \pm 0.3$  mg/ml, and total phenolic content was  $44.07 \pm 2.2$  mg gallic acid / 100 g fresh weight, respectively. Also, the study of essential oil composition showed no significant relationship between any of the compounds with antioxidant effects of these plants (9).

Shahbazi has evaluated the antioxidant effects of *Z. Clinopodioides* stems, leaves, and flowers essential oil collected from 4 western Iranian provinces (Ilam, Lorestan, Kermanshah, and Kurdistan) in DPPH radical-scavenging activity tests, Ferric reducing power,  $\beta$ -Carotene bleaching inhibition and Thiobarbituric acid. Kermanshah essential oil samples (collected from lower altitudes) showed better antioxidant effects in all tests. However, no significant difference was found between the antioxidant effects of stems, leaves, and flowers, but there was a significant difference between the antioxidant effects of essential oils collected from different provinces. The study of the essential oil compounds showed a strong role of oxygenated monoterpenes and monoterpene hydrocarbons in producing antioxidant effects. The lowest amount of oxygenated monoterpenes and monoterpene hydrocarbons obtained from Kurdistan showed the least antioxidant effects. Kermanshah oil sample had a higher DPPH radical scavenging (0.30–0.31 mg/ml), ability to prevent the bleaching of  $\beta$ -carotene (0.09–0.1 mg/ml), ferric reducing power (0.40–0.42 mg/ml) and thiobarbituric acid (0.004–0.006 Meq of malondialdehyde/g) values than that of samples from Ilam, Kurdistan, and Lorestan. The strong *in vitro* antimicrobial and antioxidant activities support the traditional use of this plant in the treatments of gastrointestinal diseases (10).

Amiri et al. investigated the chemical constituents and antioxidant effects of essential oil and methanolic extract of *Z.*

*Clinopodioides* aerial parts in DPPH radical-scavenging activity and  $\beta$ -carotene / linoleic acid tests (aerial parts were collected in spring and summer in flowering stage from Bardsir region in Kerman province in Iran). In DPPH radical-scavenging activity, methanolic extract of flower ( $IC_{50} = 0.39 \pm 0.03 \mu\text{g} / \text{ml}$ ) and methanolic extract of stem ( $IC_{50} = 1.87 \pm 0.06 \mu\text{g} / \text{ml}$ ) showed better antioxidant effects than BHT ( $IC_{50} = 2.73 \pm 0.08 \mu\text{g} / \text{ml}$ ). In the  $\beta$ -carotene / linoleic acid test, the antioxidant effects of methanolic extract of flower ( $60.60 \pm 2.49\%$  antioxidant activity) and methanolic extract of the stem ( $59.42 \pm 2.16\%$  antioxidant activity) were not significantly different from BHT ( $60.61 \pm 8.25\%$  antioxidant activity).but, the antioxidant effects of the flower essential oil ( $108.69 \pm 81.03\%$  antioxidant activity) were very significant, which seems to be due to the presence of pulegone (52.41%) in the essential oil structure. Flower extract showed the highest antioxidant activity in DPPH assay while in  $\beta$ -carotene linoleic acid, the essential oil of flower had the highest antioxidant activity (11).

Mazandarani evaluated the antimicrobial and antioxidant effects of methanolic extract of *Z. Clinopodioides* aerial parts (from the Deraznoo area of Golestan province, Iran, at an altitude of 2560 m). The antioxidant effects of methanolic extract of this plant were evaluated in total Antioxidant Capacity ( $IC_{50} = 36.7 \pm 0.3 \mu\text{g} / \text{ml}$ ), DPPH radical scavenging activity ( $IC_{50} = 32.5 \pm 0.4 \mu\text{g} / \text{ml}$ ) and reducing power assay ( $IC_{50} = 45.01 \pm 0.1 \mu\text{g} / \text{ml}$ ). BHA ( $IC_{50} = 41.05 \pm 0.3 \mu\text{g} / \text{ml}$ ) and BHT ( $IC_{50} = 35.3 \pm 0.5 \mu\text{g} / \text{ml}$ ) were used as standard in the reducing power assay test. The results also showed a positive linear relationship between antioxidant and antimicrobial effects. This paper suggested methanol extract of *Z. Clinopodioides* as a suitable antibacterial and antioxidant, which can be used as a natural anti-infective agent to treat many infectious diseases (5).

Mazandarani et al. collected the aerial parts of *Z. Clinopodioides* at the flowering stage from Bovanloo in northern Khorasan province, Iran (altitude = 1780 m). Methanolic extract

of the plant was prepared by maceration, and the antioxidant effects of this plant were evaluated in the total antioxidant capacity ( $IC_{50} = 42.5 \pm 1.3 \mu\text{g} / \text{ml}$ ), Reducing power assay ( $IC_{50} = 37.08 \pm 1 \mu\text{g} / \text{ml}$ ) and DPPH radical-scavenging activity test ( $IC_{50} = 26.5 \pm 1.4 \mu\text{g} / \text{ml}$ ). BHA ( $IC_{50} = 41.05 \pm 0.3 \mu\text{g} / \text{ml}$ ) and BHT ( $IC_{50} = 35.3 \pm 0.5 \mu\text{g} / \text{ml}$ ) were used as standards in the reducing power assay test. Evaluation of total phenolic content ( $98.13 \pm 5.9 \text{ mg gallic acid equivalent} / 100 \text{ g dried weight}$ ) and flavonoid content ( $220.9 \pm 18.65 \text{ mg quercetin equivalent} / 100 \text{ g dried weight}$ ) of methanolic extract of the plant showed the efficacy of these compounds on antioxidant effects (6). The pulegone (46.2%) was reported as the main constituent of plant essential oil. The high polyphenols content and antioxidant activities of essential oil and methanol extract of this plant can be confirmed the traditional uses of *Z. Clinopodioides* as antiinflammatory, anti-spasm, expectorant and anti-infection to treat of common cold, flu, fever, diarrhea, GI disorder and stomachache (12).

Gursoy et al. investigated the antioxidant, antimicrobial effects, and total phenolic content of 3 species of plants collected from Sivas, Turkey. The methanolic extract of the plants was prepared by the Soxhlet method at  $60^\circ\text{C}$  for 6 hours, and then their antioxidant effects were evaluated in DPPH radical-scavenging activity and  $\beta$ -carotene/ linoleic acid assay. In both tests, the best antioxidant effect was reported from methanolic extract of *Z. Clinopodioides* ( $IC_{50} = 37.73 \pm 1.18 \mu\text{g} / \text{ml}$  in DPPH Test and  $83.56 \pm 1.19\%$  inhibition rate in  $\beta$ -carotene / linoleic acid test). BHT ( $IC_{50} = 18.00 \pm 0.40 \mu\text{g} / \text{ml}$  in DPPH Test and  $96.60 \pm 1.29\%$  inhibition rate in  $\beta$ -carotene / linoleic acid test) and ascorbic acid ( $IC_{50} = 3.80 \pm 0.17 \mu\text{g} / \text{ml}$  in DPPH Test and  $94.50 \pm 1.86\%$  inhibition rate in  $\beta$ -carotene / linoleic acid test) were used as standard in this study. The highest total phenolic content was reported from *Z. Clinopodioides* methanolic extract ( $129.55 \pm 2.26 \mu\text{g} / \text{mg gallic acid equivalent}$ ). Again, a positive correlation has been reported between antioxidant activity potential and the

number of phenolic compounds in this plant (6).

Aliakbarlu et al. investigated the antioxidant, antibacterial effects, and total phenolic content of aerial parts of *Thymus Vulgaris*, *T. Kotschyanus*, *Ziziphora Tenuior* and *Z. Clinopodioides* essential oils (aerial parts of these plants were collected in summer 2011 from northwestern Iran (Urmia, Khoy, and Sanandaj). DPPH radical-scavenging activity and reducing power assay tests were used to investigate the antioxidant effects. In DPPH test, the highest amount of antioxidant activity of essential oil was reported from *Z. Clinopodioides* ( $21.51 \pm 1.4\%$  radical scavenging activity at  $2.5 \mu\text{g/ml}$  concentration) and *T. Vulgaris* ( $22.88 \pm 2.0\%$  radical scavenging activity at  $2.5 \mu\text{g/ml}$  concentration). The antioxidant effect of *Z. Clinopodioides* ( $0.791 \pm 0.09$  in  $2.5 \mu\text{g/ml}$  concentration) in reducing power assay test was significantly more than in other plants. In this study, BHT was used as the standard in both DPPH radical-scavenging activity ( $96.32 \pm 0.9\%$  radical scavenging activity at  $2.5 \mu\text{g/ml}$  concentration) and reducing power assay ( $2.553 \pm 0.11$  in  $2.5 \mu\text{g} / \text{ml}$  concentration) tests. The highest total phenolic content was reported from *T. Vulgaris* (116.47 mg GAE/g) and *Z. Clinopodioides* (114.83 mg GAE/g). Further studies revealed a positive linear relationship between total phenolic content and antioxidant effects in DPPH radical-scavenging activity ( $R^2=0.95$ ) and reducing power assays ( $R^2=0.90$ ). It has also been claimed that phenolic compounds can play an active role in producing antimicrobial effects. Finally, *Z. Clinopodioides* essential oil can be used as an excellent antibacterial and antioxidant in food preservation (13).

Rajaei et al. optimized the extraction of phenolic compounds and the antioxidant activity of *Z. Clinopodioides* ethanolic extract by ultrasound (DPPH test was used to evaluate the antioxidant activity). *Z. Clinopodioides* was collected from Shahroud in Semnan province, Iran. In this study, to optimize the extraction process, the influence of time, solvent concentration, and ratio of

solvent to dry matter were evaluated. The optimization of the phenolic compound's extraction process showed that the extraction process that took 18.29 min, 22.15% solvent concentration, and 25.95 solvent to dry matter ratio had the highest phenolic compounds extraction 7.81 mg GAE / g. The optimum conditions in terms of antioxidant activity were 6.66 min, solvent concentration 23.37%, and solvent to dry matter ratio of 14.77, in which the antioxidant activity was 14.25% per gram of primary powder. Studies showed that due to the thinner leaf of *Z. Clinopodioides*, more phenolic compounds were extracted at early times, and more extended periods had little effect on the extraction process. Also, in the early times, simpler phenolic compounds with higher hydroxyl groups and, consequently, higher antioxidant activity was first extracted. Evaluation of the results of the tests showed that the ratio of solvent to dry matter in phenolic content and time in antioxidant activity were identified as the most influential factors (14).

Salehi et al. investigated the antibacterial and antioxidant effects of essential oil and different extracts of *Z. Clinopodioides* (aerial parts of the plant were collected at the flowering stage from Tabriz, East Azerbaijan Province, Iran, in July 2003). The aqueous extract was prepared by immersing the plant in hot water for 30 minutes and then stored for 24 hours at room temperature. Acetone, ethyl acetate, and methanol extracts were prepared by maceration. Finally, the methanol extract was exposed to water and ethyl acetate to obtain water-soluble and water-insoluble fractions. The DPPH test assessed antioxidant activity. The highest antioxidant properties and total phenolic content were reported from methanol extract ( $\text{IC}_{50} = 30.7 \pm 0.6 \mu\text{g} / \text{ml}$  and  $174.8 \pm 1.2$  GAE), aqueous extract ( $\text{IC}_{50} = 34.7 \pm 0.3 \mu\text{g} / \text{ml}$  and  $166.2 \pm 3.1$  GAE), water-soluble fraction of methanol extract ( $\text{IC}_{50} = 42.3 \pm 0.6 \mu\text{g} / \text{ml}$  and  $129.2 \pm 1.1$  GAE), acetone extract ( $\text{IC}_{50} = 46.0 \pm 2.0 \mu\text{g} / \text{ml}$  and  $100.1 \pm 0.0$  GAE), ethyl acetate extract ( $\text{IC}_{50} = 47.9 \pm 1.3 \mu\text{g} / \text{ml}$  and  $95.1 \pm 0.4$  GAE), essential

oil ( $IC_{50} = 118.2 \pm 2.1 \mu\text{g} / \text{ml}$  and  $26.0 \pm 1.1$  GAE) and water-insoluble fraction of methanol extract ( $IC_{50} = 150.0 \pm 1.6 \mu\text{g} / \text{ml}$  and  $24.5 \pm 2.5$  GAE), respectively. Phenolic compounds easily release their hydrogen atoms and neutralize free radicals, which increases their antioxidant properties in the presence of phenolic compounds (3).

Tian et al investigated the antioxidant capacity, total phenolic content and flavonoid content of different *Z. Clinopodioides* extracts (whole plant was collected from Non mountain in china and evaluated). The dried powder was extracted with 90% ethanol, then extracted with Petroleum Ether, Chloroform, Ethyl Acetate, N-Butanol and Ethanol and finally dried with Freeze Dryer. In this study, antioxidant activity was evaluated by DPPH radical-scavenging activity, superoxide anion-scavenging capacity and hydroxyl radical-scavenging capacity tests. The highest amount of antioxidant activity and total phenolic and flavonoid content were reported from ethyl acetate extract ( $34.11 \pm 0.54\%$  in

DPPH,  $40.12 \pm 0.71\%$  in superoxide,  $98.27 \pm 1.43\%$  in hydroxyl,  $19.270 \pm 0.266$  TPC,  $65.610 \pm 0.826$  TFC) and the lowest amount from ether petroleum extract ( $6.97 \pm 0.09\%$  in DPPH,  $4.57 \pm 0.07\%$  in superoxide,  $7.40 \pm 0.14\%$  in hydroxyl,  $0.230 \pm 0.003$  TPC,  $11.750 \pm 0.155$  TFC). Ethanol ( $21.48 \pm 0.31\%$  in DPPH,  $29.94 \pm 0.49\%$  in superoxide,  $15.91 \pm 0.24\%$  in hydroxyl,  $1.640 \pm 0.031$  TPC,  $3.770 \pm 0.058$  TFC), n-butanol ( $28.27 \pm 0.41\%$  in DPPH,  $35.82 \pm 0.53\%$  in superoxide,  $26.14 \pm 0.42\%$  in hydroxyl,  $3.940 \pm 0.068$  TPC,  $10.760 \pm 0.132$  TFC), chloroform extracts ( $25.69 \pm 0.35\%$  in DPPH,  $20.16 \pm 0.32\%$  in superoxide,  $14.33 \pm 0.36\%$  in hydroxyl,  $4.990 \pm 0.62$  TPC,  $14.360 \pm 0.178$  TFC) also have intermediate effects. Ascorbic acid ( $32.53 \pm 0.42\%$  in DPPH,  $33.54 \pm 0.54\%$  in superoxide,  $50.01 \pm 0.79\%$  in hydroxyl) was used as standard in this study (7). A brief story of antioxidant activities of *Z. Clinopodioides* has been summarized in **Table 1**.

**Table 1. Antioxidant activities of different extracts and essential oil of *Ziziphora Clinopodioides*.**

Plant Form	Type of test	Standard	Reference
<b>Essential oil</b>	DPPH	BHT	3,11,13
		-	9,10
	$\beta$ -carotene	BHT	11
		-	10
	Reducing power assay	BHT	13
<b>Methanolic Extract</b>	Thiobarbituric acid	-	10
	DPPH	Ascorbic acid	6
		BHT	3,6,11
	$\beta$ -carotene	Ascorbic acid	5,12
	Reducing Power Assay	BHT	6,11
	BHA	5,12	
	BHT	5,12	
	Total Antioxidant Capacity	-	5,12
<b>Ethanol extract</b>	DPPH	Ascorbic acid	7
		-	14
	Superoxide anion-scavenging capacity	Ascorbic acid	7
	Hydroxyl radical-scavenging capacity	Ascorbic acid	7
<b>Water extract</b>	DPPH	BHT	3
<b>Acetone extract</b>	DPPH	BHT	3
<b>Ethyl acetate extract</b>	DPPH	BHT	3

## Conclusion

According to the results, *Z. Clinopodioides* has excellent antioxidant effects (mainly flowers). The presence of antioxidant effects in plant essential oils is due to the presence of oxygenated monoterpenes, monoterpene hydrocarbons, and pulegone compounds. Also, in most studies, the antioxidant effects of plant extracts were directly related to total phenolic content. The plant's methanolic extract appears to have the highest antioxidant properties. Finally, the essential oil and extract of the plant can be used due to its excellent antioxidant properties in antispasmodic, anti-inflammatory, anti-infective, expectorant, and in the treatment of diseases such as colds, flu, diarrhea, digestive problems and as a food preservative.

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## Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

## Authors' contributions

Study design: All authors

Writing: All authors

Final revision: All authors

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