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Determination of Phenolic Content and Biological Activity of Aqueous Extracts of *Origanum onites* L. from Different Locations

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Abstract: The phenolic content of the decoction and infusion extracts of *Origanum onites* from three different locations in Türkiye was evaluated using LC-MS/MS. The antioxidant capacity of the decoction and infusion was assessed using the 1,1-diphenyl-2-picrylhydrazyl (DPPH), *β*-carotene, linoleic acid, and CUPRAC assays. Additionally, the acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activities of both *O. onites* extracts were investigated. The highest levels of rosmarinic acid (935.79 mg/kg), penduletin (743.53 mg/kg), and kaempferol (506.14 mg/kg) were found in the decoction extract of *O. onites* from Kemer. In addition, Kemer had the highest DPPH free radical scavenging activity (61.43-75.59%) and lipid peroxidation inhibitory activity (59.03-78.99%) of all the locations examined. Kazdağı sample had the highest value on the CUPRAC assay (3.83 mmol TR g^{-1} for decoction and 3.20 mmol TR g^{-1} for infusion, respectively). The study concludes that a quantitative relationship exists between phenolic content and antioxidant activity, which is important for understanding the role of phenolics in antioxidant activity. The location had an impact on the biological activities of both *O. onites* extracts, as well as their phenolic content.

Keywords: *Origanum onites*; different location; phenolics; antioxidant; AChE; BChE.

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1. Introduction

Medicinal and aromatic plants are a valuable source of secondary compounds. They are recognized for their pharmacological properties and potential components for product development in the food industry. The Lamiaceae (Labiatae) family, one of the most important plant families, comprises approximately 230-240 genera and 7,000-8,000 species worldwide [1,2]. In Türkiye, it is represented by 45 genera and 614 species [2,3]. The Lamiaceae family comprises many medicinal and aromatic plant species valued for their culinary, medicinal, and cosmetic uses [1,4]. Recent studies have shown that many members of the Labiatae family possess high levels of biological activity, including antioxidant, antifungal, anti-cholinesterase, and antimicrobial properties [5-8].

One of the most economically important members of the Lamiaceae family is the genus *Origanum* [9]. The species are used worldwide as food, herbal tea, fodder, medicine, cosmetics, and food preservatives due to their content of terpenoids, phenolics, flavonoids, steroids, and fatty acids. [10,11]. The genus contains 42 species and is predominantly distributed around the Mediterranean, Iran-Siberian, and Euro-Siberian regions [11].

In Türkiye, the genus *Origanum* is represented by 23 species and 32 taxa [12]. The essential oil of *Origanum* species has been reported to contain high amounts of essential oil, with carvacrol and/or thymol being the primary components [13]. Studies have shown that *Origanum* species generally display remarkable activity in practically all test systems [14].

One of the most commonly used medicinal species in this family is *O. onites* L., also referred to locally as "bilyalı kekik". It is known that it is primarily utilized in infusions to treat dizziness, diabetes, high cholesterol, stomach disorders, leukemia, and hypertension, or in decoctions to treat coughs and flu [11]. Numerous studies have been conducted to investigate the phytochemical content and biological activity of *O. onites* [13, 15, 16]. However, the generality of these studies is focused on the study of essential oils, with few studies on the extracts and more particularly on the aqueous extracts, whereas infusion or decoction are the most commonly used in traditional medicine.

The literature on *O. onites* is relatively abundant. Previous studies have demonstrated that extracts of *O. onites* contain a diverse range of compounds, including terpenoids, phenolic acids, flavonoids, pigments, hydroquinones, hydrocarbons, sterols, fatty acids, and inorganic compounds [10,11]. Additionally, several extracts and individual compounds exhibited remarkable antimicrobial, antioxidant, antiviral, insecticidal, hepatoprotective, anticancer, antidiabetic, genotoxic, analgesic, anti-inflammatory, and anticholinesterase activities [10,14]. Although some studies have reported the biological activities and phenolic components of various extracts of *O. onites*, information on the *O. onites* aqueous extracts is still lacking. A previous study reported the phytochemical profile, total phenolic content, and biological activities of methanol and aqueous extracts of *O. onites* [17]. Many factors influence the chemical content and biological activity of medicinal and aromatic plants, including geographical location, environmental conditions, primary climate, soil characteristics, and cultivation practices. Therefore, we examined whether these factors relate to the production of phenolic compounds and the antioxidant capacity of *O. onites*, which is critical for its use in the food and pharmaceutical industries. The present study aims to analyze whether there are differences in phenolic content and antioxidant activity of aqueous extracts of *O. onites* at three different sites in Türkiye.

2. Materials and Methods

2.1. Chemicals

The supporting information section provides detailed data on the purity and origin of the reference materials and chemicals used in the study.

2.2. Plant Material

Fresh aerial parts of *O. onites* were collected locally from three different provinces of Türkiye: Balıkesir (Kazdağı), Muğla (Datça), and Antalya (Kemer) in June 2016. Prof. Tuncay Dirmenci identified the samples. A voucher specimen was deposited at the Herbarium of the Department of Biology Education at Balıkesir University (Table 1).

Table 1. List of the *O. onites* with locality, year, and collector number.

Collector Number	Locality	Year
Dirmenci 4711 & Yazıcı (NEF)	Balıkesir: Edremit, Kazdağı, 500-600 m	10.06.2016
Dirmenci 4713 & Yazıcı (NEF)	Muğla: Datça, Knidos Ancient City	28.06.2016
Dirmenci 4714 & Yazıcı (NEF)	Antalya: Kemer, Göynük Canyon	29.06.2016

2.3. Extractions of Samples

From the aerial parts of the plant, 4 g of sample was dried in the shade and chopped into small pieces. The aqueous extracts were prepared using two methods: infusion and decoction.

Infusion: 2 g of the plant was added to 98 mL of distilled boiling water and left to stand for 15 minutes. Decoction: 2 g of the plant was added to 98 mL of distilled water and heated together in a steel kettle. After boiling, the mixture was left to stand for 15 minutes. The aqueous extracts were filtered with an ashless filter paper. They were diluted with 25 mL of distilled water.

2.4. General

LC-MS/MS experiments were performed using Zivak® HPLC and Zivak® Tandem Gold Triple Quadrupole (Istanbul, Turkiye) mass spectrometry, which is equipped with a Troyasil C18 column (250 x 2.1 mm i.d., 5-µm particle size). The compounds used as standards in the LC-MS/MS analyses are detailed in the supplementary material.

The absorbance (in the UV and visible range, 230 nm to 750 nm) was measured using a multiplate reader (Beckman Coulter DTX 880 Multimode Detector) to assess the antioxidant and anticholinesterase activities.

2.5. Biological Activity

The inhibitory activities of acetylcholinesterase and butyrylcholinesterase were measured using a slightly modified spectrophotometric method developed by Ellman, Courtney, Andres, and Featherston [18]. Acetylthiocholine iodide and butyrylthiocholine iodide served as substrates for the reaction, and the DTNB method was utilized to measure anticholinesterase activity [18,19]. The antioxidant capacities of aqueous extracts were measured based on 2,2-Diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity, *β*-carotene linoleic acid assays, and cupric (Cu^{2+}) ion-reducing power assay (CUPRAC) [20–23]. The procedures for determining the activities are outlined in the supplementary material.

3. Results and Discussion

3.1. Phenolic Contents

The changes in the qualitative and quantitative composition of phenolic compounds of *O. onites* at three different locations from Kazdağı, Datça, and Kemer are given in Table 2. The main constituents of the *O. onites* aqueous extracts were identified by LC-MS/MS measurements as rosmarinic acid (935.79-309.32 mg/kg), kaempferol (506.14-154.26 mg/kg), penduletin (743.53-128.19 mg/kg) by LC-MS/MS measurements (Figure 1). Following these compounds, quercitrin, caffeic acid, quercetagetin-3,6-dimethyl ether, and chlorogenic acid were determined as the most abundant components.

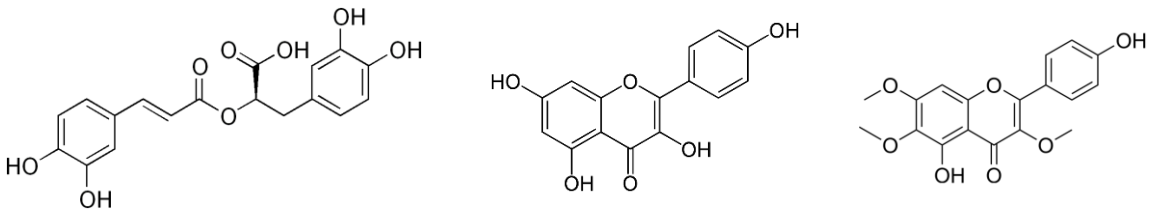
As shown in Table 2, decoction of *O. onites* from Kemer (4629.57 mg/kg) presents the highest content of phenolic compounds, followed by the infusion of *O. onites* from Kazdağı (1974.99 mg/kg) and decoction of *O. onites* from Daçta (1913.92 mg/kg). A significant difference was observed between the decoction and infusion of *O. onites* from Kemer in phenolic content. Still, the differences between decoctions and infusions of *O. onites* from Kazdağı and Datça were not significant. Some studies are reporting the phenolic content of various extracts of *O. onites* species. Pizzale et. al. (2002) reported the presence of caffeic acid and rosmarinic acid in *O. onites* methanolic extracts [24]. The total phenolic content, antioxidant, enzyme inhibitory, and antibacterial capacities of methanol and aqueous extracts of *O. onites* were investigated [17]. Ozkan et. al. reported that *O. onites* can be considered as a good source of phenolic compounds such as rosmarinic acid and acecetin [25]. Additionally, the chemical composition, total phenolic, total flavonoid contents, and antioxidant activity of the ethanol extract of

O. onites collected from Muğla, Türkiye, were investigated. Naringenin, apigenin, caffeic acid, and fumaric acid were abundant in the extract [26].

Table 2. Phenolic contents of the decoction and infusion of aqueous extracts of *O. onites* from three different locations (Kazdağı, Datça, and Kemer).

		Decoction			Infusion		
No	**Compounds**	**Kazdağı**	**Datça**	**Kemer**	**Kazdağı**	**Datça**	**Kemer**
1	Pelargonin	74.9±7.62	133.56±13.59	333.59±33.95	72.6±3.69	162.33±8.26	96.69±4.92
2	**Kaempferol**	**417.32±29.45**	**221.14±15.61**	**506.14±35.72**	**334.73±23.63**	**154.26±10.89**	**196.69±13.88**
3	Salvigenin	5.1±0.35	-	47.18±3.21	2.26±0.15	-	-
4	**Penduletin**	**328.34±33.29**	**392.29±39.77**	**743.53±75.38**	**296.2±30.03**	**332.51±33.71**	**128.19±13**
5	Quercitrin	81.14±5.18	48.32±3.08	164.63±10.5	55.2±3.52	40.1±2.56	78.17±4.99
6	Fumaric acid	-	186.04±12.9	419.86±29.12	264.21±18.32	243.44±16.88	231.56±16.06
7	Pyrogallol	-	-	-	9.81±0.65	10.07±0.67	-
8	Caffeic acid	62.23±12.31	108.06±21.38	120.37±23.82	53.14±10.52	64.71±12.8	54.54±10.79
9	t-ferulic acid	-	-	5.57±0.39	-	45.03±3.15	132.77±9.28
10	Syringic acid	3.62±0.24	7.43±0.5	-	3.12±0.21	3.28±0.22	1.72±0.12
11	Apigenin	37.44±3.02	73.59±5.93	145.77±11.74	38.59±3.11	90.02±7.25	67.45±5.43
12	Luteolin	31.01±7.96	40.89±10.5	376.37±96.68	65.62±8.43	92.84±11.92	131.14±16.84
13	Isorhamnetin	-	-	25.97±2.29	1.02±0.09	-	-
14	Quercetagetin-3,6-dimethylether	57.51±10.77	113.24±21.2	43.11±8.07	45.03±8.43	52.06±9.75	9.11±1.71
15	Chlorogenic acid	46.44±6.43	20.67±2.86	65.44±9.06	121.23±16.79	25.38±3.51	32.44±4.49
16	**Rosmarinic acid**	**596.58±45.74**	**481.08±36.89**	**935.79±71.76**	**477.56±36.62**	**386.45±29.63**	**309.32±23.72**
17	Luteolin-7-glucoside	7.54±0.77	49.8±5.07	400.44±40.75	5.54±0.28	44.81±2.28	135.4±6.89
18	Luteolin-5-*O*-Glucoside	76.59±4.93	27.44±1.77	306.18±19.7	66.51±4.28	19.53±1.26	75.00±4.83
19	Kaempferol-3-*O*-Rutinoside	-	-	-	7.37±0.67	-	-
	Total (mg/kg)	**1825.76**	**1913.92**	**4629.57**	**1974.99**	**1766.82**	**1778.32**

Among the studied aqueous extracts, decoction of *O. onites* from Kemer location indicates a high amount (935.79 mg/kg) of rosmarinic acid, followed by decoction of *O. onites* from Kazdağı (596.58 mg/kg). Kaempferol was determined as the second most abundant phenolic content in both extracts of *O. onites* from Kazdağı and Kemer, while penduletin was detected in both extracts of *O. onites* from Datça. Pyrogallol and kaempferol-3-*O*-rutinoside were not detected in the decoction of *O. onites* from Kazdağı, Datça, and Kemer locations. Isorhamnetin was detected only in the decoction of *O. onites* from Kemer, with a value of 25.97 mg/kg, and in the infusion from the Kazdağı location, with a value of 1.02 mg/kg.



Rosmarinic acid Kaempferol Penduletin

Figure 1. The structures of the three most abundant phenolic compounds in the extracts.

Rosmarinic acid has been isolated from many taxa of the Lamiaceae (*Lavandula, Melissa, Mentha, Micromeria, Monarda, Origanum, Salvia, Satureja*, etc.) [27-29]. Rosmarinic acid is known to have antioxidant, anti-angiogenic, antifibrotic, anti-inflammatory, and anticancer activity [30,31]. Rosmarinic acid has been shown to protect against primary DNA damage, skin damage from UVB light, atopic dermatitis, retinopathy treatment, rheumatoid arthritis, and various types of human cancers that are resistant to chemotherapy [30].

3.2. Biological Activity

The antioxidant potential of aqueous extracts was defined by *β*-carotene linoleic acid, DPPH free radical scavenging and CUPRAC assays in vivo. *β*-carotene bleaching and DPPH free radical scavenging effects were assessed at 2, 5, 10, and 20 µL, and the results are shown in Table 3. BHA and BHT served as standard compounds in each antioxidant assay and *O. onites* exhibited stronger activity than BHA (with an inhibition activity of 20.11-62.39%), while BHT demonstrated better activity than the aqueous extracts (72.51-80.82%). Decoction extracts were found to be more active than the infusion extracts. A positive relationship exists between DPPH values and the phenolic content of *O. onites* from Datça and Kemer. According to the results of the *β*-carotene bleaching assay, *O. onites* was found to exhibit moderate antioxidant activity (41.05%-78,99% inhibition). In contrast, standard compounds were found to be stronger antioxidant in this assay (BHA: 51.79%-85.98%, BHT: 71.02%-82.56%). In the CUPRAC method, decoction and infusion of *O. onites* showed good antioxidant activity compared to the standard compound as well. Decoction extract of *O. onites* was found to exert better activities than the infusion extract (Figure 2). Among the infusion samples of *O. onites*, Kazdağı exhibits the highest CUPRAC activity. This is because the infusion of *O. onites* obtained from Kazdağı has the highest phenolic content.

According to the results, at 200 µg/mL concentration, decoction and infusion of *O. onites* from three different locations showed weak butyrylcholinesterase (BChE) inhibitory activity with a rate range 36.20 ± 0.97 % - 50.85 ± 3.91 %, and moderate acetylcholinesterase (AChE) inhibitory activity with 50.96 ± 1.46 % - 60.46 ± 3.19 % compared to the standard compound galantamine (77.13 ± 4.31 % and 86.73 ± 5.25 %, respectively) (Table 4). The decoction of *O. onites* from the Kazdağı location exhibited better AChE (60.46 ± 3.19 %) inhibitory activity. This may be attributed to the high chlorogenic acid content of the *O. onites* decoction from Kazdağı. Oboh et al. (2013) reported that chlorogenic acid inhibited AChE and BChE, thereby suggesting a new treatment modality for Alzheimer's disease [32].

There are a few studies on the anticholinesterase activity of essential oil and various extracts of *O. onites*. The essential oil of *O. onites* appeared to be quite effective against AChE and BChE enzymes (96.3% and 92.9%, respectively) compared to galantamine (99.8% and 80.3%, respectively) [33]. In another study, the ethanol extract of *O. onites* showed weak acetylcholinesterase inhibitory activity and moderate butyrylcholinesterase inhibitory activity compared to the standard compound [26]. These findings align with the literature.

Table 3. DPPH free radical scavenging activity and lipid peroxidation of the extracts, BHA, and BHT

DPPH Assay (Inhibition%)								
	Decoction				**Infusion**			
O. onites	**2 µL**	**5 µL**	**10 µL**	**20 µL**	**2 µL**	**5 µL**	**10 µL**	**20 µL**
Kazdağı	74.50±0.17	73.05±0.97	72.13±0.36	73.95±0.72	61.40±1.80	63.44±3.69	66.77±2.36	56.94±2.15
Datça	75.74±1.04	75.51±1.09	75.18±1.05	74.82±1.65	60.89±2.68	62.49±3.15	66.17±1.29	64.76±1.64
Kemer	75.59±0.54	74.53±0.61	74.13±0.42	74.85±0.60	63.77±2.46	61.43±1.85	61.73±2.97	65.17±0.43
BHA	22.75±2.15	30.97±4.14	48.17±3.94	62.39±2.99	20.40±0.87	21.34±0.89	20.11±0.48	20.64±1.05
BHT	72.51±2.69	76.45±1.59	77.91±0.51	79.22±1.02	73.09±2.62	77.68±0.74	78.79±0.76	80.82±1.56
***β*-carotene-Linoleic Acid Assay (Inhibition%)**								
	Decoction				**Infusion**			
O. onites	**2 µL**	**5 µL**	**10 µL**	**20 µL**	**2 µL**	**5 µL**	**10 µL**	**20 µL**
Kazdağı	52.32±11.40	73.89±7.27	66.25±8.32	67.62±2.29	72.98±4.99	74.34±5.39	72.87±7.35	60.90±3.62
Datça	41.05±7.58	70.28±10.68	64.08±13.07	70.95±2.30	68.27±3.18	68.26±15.9	70.66±10.86	62.22±1.53
Kemer	59.03±19.82	74.94±8.68	69.32±13.73	78.99±2.13	59.54±6.28	69.78±4.14	73.47±2.04	66.30±1.38
BHA	61.79±4.04	59.05±5.69	51.79±3.32	65.99±6.17	81.90±1.95	85.54±1.73	85.98±2.42	79.54±4.13
BHT	73.37±4.25	72.71±2.09	74.98±5.33	73.25±1.74	82.56±5.03	72.38±11.8	77.12±2.93	71.02±1.01

To date, numerous studies have highlighted the positive effects of phenolic compounds in neurodegenerative diseases due to their antioxidative potential. However, there are limited reports showing the acetylcholinesterase and butyrylcholinesterase inhibitory activities of phenolics [34].

Compared to other studies in the literature, these results demonstrate that the decoction and infusion of *O. onites* exhibit significantly more effective antioxidant properties. The antioxidant potential of the *O. onites* decoction correlates with the higher phenolic content found in this extract compared to the infusion.

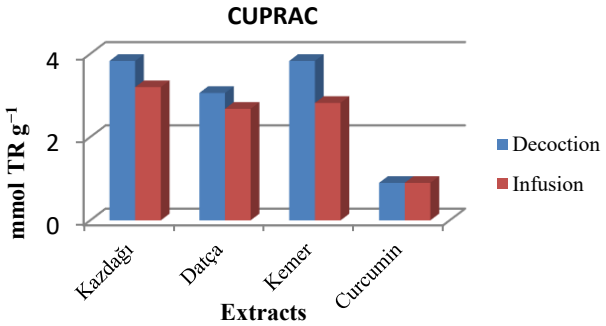


Figure 2. Cu^{2+} reducing power (CUPRAC) assay of decoction and infusion of *O. onites* and curcumin.

In recent studies, phenolic compounds have been found to have diverse effects, including antioxidant, antimicrobial, anticarcinogenic, and anti-inflammatory properties [35]. The pharmacological activities of these compounds are mainly based on their hydroxyl groups and molecular shape [36]. Phenolic compounds have excellent antioxidant effects, demonstrating their activity by preventing the harmful effects of reactive oxygen species (ROS) and free radicals on biomolecules. Additionally, rosmarinic acid, identified as the primary phenolic compound in *O. onites* extracts, has been reported to exhibit higher antioxidant activity. Antioxidants play an important role in preventing or treating degenerative diseases, including Alzheimer's disease [37]. Rosmarinic acid contains four aromatic -OH groups that can be reduced, enhancing the molecule's strength as an antioxidant agent. The reports obtained from a study support the idea that rosmarinic acid has potential biological activity for treating Alzheimer's disease [37]. In another study, kaempferol demonstrated superior antioxidant activity against ABTS free radicals compared to BHT and vitamin C [38]. Also, research indicates that kaempferol and its glycosylated derivatives have a neuroprotective function in various types of neurodegenerative disorders, including Alzheimer's disease [36]. In conclusion, the radical scavenging capacity of phenolic compounds is particularly important for preventing damage caused by reactive oxygen species (ROS) and free radicals in food applications. Additionally, these findings demonstrate the potential of decoction and infusion of *O. onites* as a novel source of phenolic compounds that may be utilized as a functional food to contribute to overall health benefits.

Table 4. Anticholinesterase activity of the decoction and infusion of *O. onites*

	AChE % Inhibition (200 µg/mL)		BChE % Inhibition (200 µg/mL)	
O.onites	**Decoction**	**Infusion**	**Decoction**	**Infusion**
Kazdağı	53.94±4.80	60.46±3.19	41.24±2.46	45.28±2.97
Datça	52.62±4.25	53.37±3.96	43.76±3.70	50.85±3.91
Kemer	53.32±4.79	50.96±1.46	45.05±2.19	36.20±0.97
Galantamine*	86.73±5.25		77.13±4.31	

*Positive control.

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Supporting Information

Supporting information accompanies this paper on https://www.acgpubs.org/journal/records-of-agricultural-and-food-chemistry

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