Investigation of Urease and Xanthine Oxidase Inhibition and the Antioxidant Properties of Lamium orientale, along with its Essential Oil Composition

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Abstract

This study aimed to investigate the anti-urease and anti-xanthine oxidase (XO) activities, essential oil components, and antioxidant properties of *Lamium orientale* populations in the Nevşehir Province, Turkey. The methanolic extracts of *L. orientale* were tested for their inhibitory effects on the urease and XO enzymes. Essential oil components were analyzed using solid-phase microextraction (SPME), followed by gas chromatography-mass spectrometry (GC-MS). Antioxidant potential was assessed by measuring total phenolic content (TPC), ferric reducing antioxidant power (FRAP) assay, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity. Results showed that *L. orientale* exhibits significant enzyme inhibitory potential, with IC_{50} values of 39.54 ± 0.98 µg/mL for anti-urease activity and 28.05 ± 0.88 µg/mL for anti-XO activity. Essential oil analysis identified 22 components, with acetoin (20.80%) and pentadecanolide (14.21%) as the main constituents. The total phenolic content was 4.48 ± 0.08 mg GAE/g of dry sample. The FRAP value was 59.33 ± 0.90 µmol $FeSO_4$/g, and the DPPH radical scavenging activity (IC_{50}) was 0.63 ± 0.01 mg/mL. This is the first study to report the inhibition potential of urease and xanthine oxidase (XO) in the genus *Lamium*, highlighting the potential of *L. orientale* as a source of new bioactive compounds.

Introduction

Urease and xanthine oxidase (XO) are essential enzymes involved in various metabolic processes. Urease catalyzes the hydrolysis of urea to carbon dioxide and ammonia (Özil et al. 2021; Saral et al. 2024; Saral and Karaköse 2024). Increased urease activity can disrupt the pH balance in the stomach and intestines and lead to the development of various infections (e.g., Helicobacter pylori) (Özil et al. 2021; Yang et al. 2023). Xanthine oxidase (XO) is an enzyme that oxidizes hypoxanthine to xanthine and xanthine to uric acid (Huang et al. 2022). High xanthine oxidase activity can lead to elevated uric acid levels in the blood, which in turn can contribute to various pathological conditions, including gout, kidney stones, and cardiovascular diseases (Aladdin et al. 2020; Rullo et al. 2023). Therefore, identifying inhibitors of these enzymes is important for developing new treatment strategies.

For millennia, the utilization of flora as a crucial source of sustenance and therapeutic agents has been instrumental in the survival and well-being of human populations (Karaköse 2022). Contemporary medicine and pharmacology are engaged in research endeavors aimed at identifying effective, natural, and reliable agents to combat complex health issues, such as cancer and metabolic diseases (Saral et al. 2024). The focal point of these studies is the analysis of phytochemicals, which are the secondary metabolites produced by plants. These phytochemicals encompass a diverse group of compounds, including phenolic compounds, flavonoids, and terpenoids (Saral and Karaköse 2024).

The Lamiaceae family is a diverse group of flowering plants comprising 268 genera and approximately 8,140 species worldwide (WFO 2025). This family is widespread and remarkably diverse in warm and temperate regions. It is one of the richest plant families in terms of bioactive compounds (Yaylı et al. 2014; Çelik et al. 2021). The family comprises mostly herbs, occasional trees, and shrubs, and has

significant economic and medicinal importance. Members of this family are commonly used as spices, teas, and traditional medicines, and are also utilized as food and ornamental plants (Selvi et al. 2022). Numerous scientific studies have shown that species in this family exhibit a wide range of biological activities, including antioxidant, anti-inflammatory, and anticancer properties. A substantial body of scientific research has demonstrated that species belonging to this family exhibit a wide range of biological activities, including antioxidant, anti-inflammatory, and anticancer properties (Çelik et al. 2021).

Lamium orientale (Fisch. & C.A.Mey.) E.H.L. Krause, belonging to the genus *Lamium* L. and formerly known as *Wiedemannia orientalis* Fisch. & C.A.Mey. (WFO 2025), is an herbaceous plant that grows up to 7–35 cm tall. It is native to the Iran-Turan phytogeographic region and is commonly referred to as "Eastern ballıbaba" (Güner et al. 2012). The plant is widely distributed throughout Anatolia and is a notable member of this family. *Lamium orientale* has a stem that is dense, sparse, soft, and covered with short hairs. Its leaves are stalked at the base and sessile in the upper part. Leaf blades are broadly ovate, ovate-lanceolate, or oblong, with entire, serrated, or rarely coarsely toothed margins. The flowering period occurs between April and June, during which the flowers display colors such as pale deep pink, light purple, and lavender. The lower lip of the flower was darker and often showed a spotted pattern. This species is found in a variety of environments, including rocky hills at elevations ranging from 700 to 1,650 meters above sea level, as well as steppes, fields, vineyards, and roadside areas (Mill 1988).

Lamium orientale has a long history in traditional medicine in Anatolia, dating back to ancient times. Local communities employ a traditional remedy that involves consuming tea prepared from the plant's flowers to manage diarrhea (Kadıoğlu et al. 2021). The plant is also known to possess laxative and tonic properties (Çakılcıoğlu et al. 2007). It is used to treat various diseases, including digestive disorders, menstrual irregularities, and inflammation of the prostate and urinary tract (Doğan and Bağcı 2011). The nectar found beneath the petals of this plant, known as "emzik otu" in Amasya, is consumed by the local population (Cansaran and Kaya 2008).

Lamium orientale has been demonstrated to possess various biological activities, as indicated by scientific studies, in addition to its traditional uses. In a recent study, 26 bioactive compounds were identified among the 38 polyphenols. Among these compounds, chlorogenic acid was found at the highest concentration. In addition, flavonoids, including rutin, hyperoxide, and isoquercitrin, are present in significant amounts (Tüfekçi et al. 2025). Extensive research has confirmed the strong antioxidant capacity of *Lamium orientale* extract. This activity is attributed to the high levels of phenolic and flavonoid compounds found in the flowers and leaves of the plant. The effectiveness of this antioxidant activity has been validated through various tests, including the DPPH and ABTS methods (Albayrak and Aksoy 2013; Türkoğlu 2018; Keser et al. 2022; Tüfekçi et al. 2025). The plant's anticancer potential is promising. It has been shown that this substance has cytotoxic effects against breast cancer (MCF-7) cell lines. Root extracts are reported to be the most effective, demonstrating high anticancer activity against colon (HCT-116) and prostate (LNCaP) cancer cells (Keser et al. 2022; Tüfekçi et al. 2025).

The results of different studies on the antimicrobial activity of Lamium orientale vary. Although some studies have shown that plant extracts have strong antibacterial effects against both Gram-positive and Gram-negative bacteria, a more recent and comprehensive study did not find any significant activity against the tested bacterial species (Albayrak and Aksoy 2013; Türkoğlu 2018; Keser et al. 2022; Tüfekçi et al. 2025).

Although only a limited number of studies exist (Albayrak and Aksoy 2013; Tüfekçi et al. 2025), observations suggest that *L. orientale* inhibits certain key enzymes. Extracts from the plant's roots have been shown to inhibit the activity of enzymes such as acetylcholinesterase, tyrosinase, amylase, and *β*-glucosidase, which are associated with conditions including Alzheimer's disease, skin discoloration, and diabetes (Tüfekçi et al. 2025). Additionally, the plant's extracts have been shown to inhibit the formation of bacterial biofilms. A study found that both root and leaf extracts significantly inhibited biofilm formation by *Pseudomonas aeruginosa* bacteria (Tüfekçi et al. 2025).

The chemical composition and biological activity of *L. orientale* vary depending on factors such as soil conditions, climate, harvest season, and the growing environment. This study aimed to determine the anti-urease and anti-XO activities, essential oil components, and antioxidant activity of *Lamium orientale* populations in the Nevşehir Province, Türkiye.

Materials and Methods

Plant Sample

Samples of *Lamium orientale* were collected in Turkey during the 2017 vegetation season (*L. orientale*: (Derinkuyu/Nevşehir, 1210 m, 16.05.2017, 38°21'26"N 34°44'11"E, MK-1614). Associate Professor Dr. Mustafa Karaköse, a botanist, identified and confirmed the plant. The voucher specimen was subsequently deposited at the Espiye Vocational School at Giresun University. The collected plants were dried and ground at room temperature. The samples were then stored in a refrigerator at + 4°C until analysis.

Preparation of Extracts

Five grams of the dry sample were weighed, and 25 mL of methanol was added. The mixture was then stirred for 24 h using a magnetic stirrer. The mixture was then filtered through Whatman filter paper. The filtrate was stored in a refrigerator at + 4°C until further analysis (Saral et al. 2024).

Inhibitory activity of urease and xanthine oxidase

XO inhibition was measured using UV spectroscopy at 295 nm, which corresponds to the release of uric acid from xanthine. The extract's inhibitory activity was assessed using established reference methods (Baltaş et al. 2016; Akyüz Turumtay et al. 2023). Allopurinol was used as a positive control in the

inhibition test. The IC_{50} value was determined as the concentration of the compound that inhibited 50% of its maximum activity. Urease catalyses the hydrolysis of urea into carbon dioxide and ammonia. Ammonia production was measured using the indophenol method to evaluate urease inhibitory activity. Results were expressed as IC_{50} values, indicating the concentrations needed to inhibit substrate hydrolysis, derived from the dose–response curve. Acetohydroxamic acid was used as the reference compound in the urease inhibition test (Kantar et al. 2015; Baltaş et al. 2016). All experiments were conducted in triplicate to calculate the standard deviation.

SPME procedure and GC-MS analysis

A dry plant sample (two grams) was placed in a 10 mL vial, and then a fiber coating was applied to the headspace. An SPME fiber (polydimethylsiloxane/divinyl-benzene, Supelco, USA) was conditioned for 5 min at 250°C using a gas chromatography (GC) injector. The SPME analysis was conducted at 80°C with an incubation period of 5 min and an extraction time of 10 min. Essential oil analysis was performed on a Shimadzu QP2010 Plus gas chromatography (connected to a Shimadzu QP2010 Ultra mass selector detector) using an HP-5MS capillary column (30 m × 0.25 mm, film thickness 0.25 µm). The SPME fiber was introduced into the injection port of the GC-MS. The oven temperature was programmed to remain at 60°C for 2 minutes, and then increased at a rate of 3°C/min to a final temperature of 250°C. The column flow rate was set to 1.0 mL/min, with helium (99.999%) used as the carrier gas. The mass spectrometer was operated over the range of 40–400 m/z at an electron voltage of 70 eV. The essential compounds were identified by comparing the mass spectra to those of two libraries (FFNSC1.2 and W9N11) (Fandaklı et al. 2019).

Determination of total phenolic content and antioxidant activity

The total phenolic content (TPC) was measured using the Folin-Ciocalteu assay. Gallic acid was used as the reference standard (Slinkard and Singleton 1977). The FRAP assay was conducted to assess the total antioxidant capacity of the samples using a standard solution of ferric sulfate (FeSO4) (Benzie and Szeto 1999). The radical scavenging activity was evaluated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) as a stable radical (Molyneux 2004). Trolox served as the standard, with the concentrations expressed as IC_{50} (mg samples/mL). All tests were performed in triplicate. The reagents and solutions used were freshly prepared.

Statistical analysis

Statistical analyses were not performed. All tests were conducted in triplicate, and the results are presented as the mean and standard deviation.

Results

Anti-urease and anti-XO activity

The anti-urease and anti-XO activities of *L. orientale* are shown in Table 1. The anti-urease activity was 39.54 ± 0.98 µg/mL, and the anti-XO activity was 28.05 ± 0.88 µg/mL.

Table 1
Enzyme inhibition results of *L. orientale*

IC_{50} value of urease and XO activity% ±SD[a]		
	Urease inhibition (µg/mL)	XO inhibition (µg/mL)
L. orientale	39.54 ± 0.98	28.05 ± 0.88
[b]Acetohyroxamic Acid	27.01 ± 0.06	-
[c]Allopurinol	-	0.055 ± 0.01
[a]standard deviation (n = 3), [b]reference for urease inhibition; [c]reference for XO inhibition		

Essential oil composition

The chemical composition of the essential oil of *L. orientale* was analyzed using SPME and GC-MS. Table 2 presents the results. A total of 22 compounds were identified in the essential oil of *L. orientale*. The major essential oil compounds were acetoin (20.80%) and pentadecanolide (14.21%). The essential oil of *L. orientale* was characterized by its high hydrocarbon content (33.56%).

Table 2
Compounds in the essential oils of *L. orientale*

No	Essential oil components	*Lamium orientale* (%)	RI (Exp)[a]	RI (Lit)[b]
	Aldehydes			
1	Hexanal	1.07	804	800
2	Pentanal	0.73	979	984
3	Tetradecanal	1.18	1614	1611
	Ketone			
4	Acetoin	**20.80**	711	706
	Alcohol			
5	2-ethylhexanol	4.93	1030	1026
	Ether			
6	Anethole	1.36	1282	1283
	Hydrocarbons			
7	Hendecane	0.74	1065	1102
8	Dodecane	1.81	1208	1200
9	Tridecane	2.67	1299	1291
10	Tetradecane	7.90	1406	1399
11	Pentadecane	3.43	1507	1499
12	Hexadecane	1.54	1599	1601
13	Heptadecane	2.22	1705	1709
14	Octadecane	8.31	1793	1799
15	Eicosane	1.08	1998	2000
16	Docosane	3.86	2197	2200
	Lactones			
17	δ-Undecalactone	1.70	2216	2264
	Pentadecanolide	**14.21**	1841	1839
	Esters			

[a]RI was calculated from retention times relative to that of alkanes (C7-C30) on the HP-5MS column.
[b]RI based on literature (https://webbook.nist.gov/)

No	Essential oil components	*Lamium orientale* (%)	RI (Exp)[a]	RI (Lit)[b]
18	Ethyl pyruvate	1.80	1242	1253
19	Dihydromyrcenyl acetate	2.69	1204	1202
	Terpen			
20	Verbenone	0.80	1207	1209
	Fatty Acids			
21	Valeric acid	0.81	882	887
22	Hexadec-6-enoic acid	1.14	2104	2103
	Unknown	13.22		
	Total	**100**		

[a]RI was calculated from retention times relative to that of alkanes (C7-C30) on the HP-5MS column.
[b]RI based on literature (https://webbook.nist.gov/)

Total phenolic content and antioxidant activity

Table 3 shows the total phenolic content, FRAP, and DPPH values of *L. orientale*. The total phenolic content was measured as 4.48 ± 0.08 mg GAE/g dry sample. The antioxidant capacity of the methanol extract, as assessed by the FRAP method, was 59.33 ± 0.90 µmol FeSO4/g. The radical scavenging activity, determined using the DPPH method, showed a value of 0.63 ± 0.01 mg/mL.

Table 3
TPC, FRAP, and DPPH values for *L. orientale*

Sample	TPC (mg GAE/g)	FRAP (µmol $FeSO_4$/g)	DPPH (IC50:mg/ mL)
L. orientale	4.48 ± 0.08	59.33 ± 0.90	0.63 ± 0.01

Discussion

Helicobacter pylori is involved in the development of peptic ulcers and stomach cancer. It is protected from stomach acid by the urease enzyme it secretes (Özil et al. 2021; Saral et al. 2024). Therefore, inhibition of urease is crucial for the treatment of *H. pylori*-related diseases. In this study, urease inhibition was measured at 39.54 ± 0.98 µg/mL (Table 1). A lifestyle and diet high in purines are directly associated with increased uric acid levels. To reduce uric acid levels, it is necessary to inhibit XO, an enzyme essential for uric acid production (Mehmood et al. 2022). Table 2 shows the inhibitory effects of *L. orientale* and the positive control allopurinol against xanthine oxidase. The IC_{50} value of *L. orientale* was 28.05 ± 0.88 µg/mL. Several studies have explored the urease and XO inhibitor potential of various plants (Khan et al. 2014; Aladdin et al. 2020; Medina-Pérez et al. 2021; Ashibuogwu et al. 2022; Huang et

al. 2022; Saral et al. 2024). No research has been published on the urease and XO inhibition potential of *Lamium* species, making this the first study to address this topic.

In recent years, numerous studies have been conducted to identify essential compounds in food products or plants. Essential oils are used to extend the shelf life of foods and beverages owing to their antioxidant and antimicrobial properties (Xing et al. 2019). Hydrodistillation is commonly used in these studies to extract essential oils. Recently, SPME, a faster, solvent-free technique, has been employed (Yang et al. 2023). GC-MS was used to analyze the essential oil composition of *L. orientale* using SPME. In our study, 22 volatile compounds were identified, with acetoin and pentadecanolide being the main components. The primary components in the essential oil obtained by hydrodistillation from the aerial parts of *Wiedemannia orientalis* (a synonym of *L. orientale*) were germacrene D (38.94%), geijeren (14.60%), and pregeijeren (12.90%) (Başer et al. 1996). In a separate study, it was reported that the main components in the essential oil obtained through hydrodistillation of *W. orientalis* were germacrene D (23.3%), thymol (16.4%), and carvacrol (12.3%) (Kılıç and Bağcı 2014). However, these components were not detected in this study. We believe that this difference was due to the extraction method used. Additionally, the studies differed in the years and regions where the plant was collected.

Phytochemicals, natural antioxidants found in plants, have been widely studied, and research in this area continues to expand (Tüfekçi et al. 2025). Various analytical methods have been used to assess the phenolic content and antioxidant activity of plants. In this study, the total phenolic content of *L. orientale* was measured. Additionally, FRAP and DPPH assays were conducted to assess antioxidant capacity (Table 3). According to Albayrak and Aksoy (2013), the TPC of the aerial parts of *L. orientale* was 9.53 ± 0.00 mg GAE/g sample, while the DPPH test yielded a value of 87.22 mg/mL using BHT as the standard. In contrast, Keser et al. (2022) reported a much higher TPC value of 124.54 ± 0.97 mg GAE/g sample. Concurrently, the DPPH radical scavenging activity was reported as 91.60 ± 0.05%. The previously reported TPC values were higher than those obtained in the present study. However, we could not compare these results because of differences in the standards and units used in DPPH activities. Some studies in the literature have analyzed the leaf, flower, and stem parts of *L. orientale* separately. One study examining the leaf and flower parts found the total phenolic content of the leaf to be high (17.27 ± 0.09 mg GAE/g sample). Interestingly, DPPH activity is high in flowers (Türkoğlu 2018). In a recent study, roots, stems, leaves, and flowers of *L. orientale* were evaluated. The flower exhibited high activity in TPC (35.9 ± 0.3 mg GAE/g), FRAP (71.2 ± 0.6 mg TE/g), and DPPH (79.9 ± 1.2 mg TE/g) assays (Tüfekçi et al. 2025).

Conclusion

This study revealed that methanolic extracts of *Lamium orientale* exhibited significant inhibitory activities against urease (IC_{50}: 39.54 µg/mL) and xanthine oxidase (IC_{50}: 28.05 µg/mL). These findings suggest that this plant could be a potential source of natural remedies for conditions associated with hyperuricemia, such as Helicobacter pylori infection and gout. To our knowledge, this is the first study to investigate these enzyme-inhibitory activities in the genus Lamium. Additionally, this is the first report of

acetoin and pentadecanolide as the major components of the plant's essential oil profile. These results differ from those of previous research because of variations in the extraction method (SPME) and geographical origin. The plant also demonstrated notable antioxidant properties. The obtained data confirm that L. orientale grown in Nevşehir is a promising candidate for further research focused on developing natural antioxidants and enzyme inhibitors for use in the pharmaceutical and food industries.

Declarations

Conflicts of Interest:

The authors declare no conflict of interest.

Author Contributions:

Ö.S. and M.K. conceived and initiated the work. M.K. harvested plant material, Ö.S. performed the extraction experiments, and drafted the manuscript. Ö.S. and N.B. performed the chemical analysis experiments. All of the authors critically edited the manuscript before submission.

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