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# Phenological Stage Dependent Variations in the Chemical Composition and Cyclooxygenase (COX) Inhibitory Activities of *Origanum dubium* Boiss. Essential Oils

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## ABSTRACT

This study investigated the essential oil yield, chemical composition, and COX-1/2 inhibitory activity of *Origanum dubium* during different developmental stages. Essential oil yield increased from 5.53% to 8.37%, peaking at the post-flowering stage. Chemical analysis revealed that oxygenated monoterpenes dominated the oil composition, with carvacrol as the principal component, increasing significantly from 64.4% to 86.9% across growth stages. The anti-inflammatory potential was evaluated by measuring COX-1/2 inhibitory activity, using ibuprofen as a positive control (73.53% inhibition). Essential oils exhibited moderate inhibition during vegetative (52.13%) and initial flowering (57.76%) stages, but inhibition notably improved at post-flowering (68.16%), approaching ibuprofen's efficacy. These findings suggest that the rise in carvacrol concentration correlates with enhanced COX-1/2 inhibitory activity, highlighting the therapeutic potential of *O. dubium* essential oils as natural anti-inflammatory agents.

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# *Origanum dubium* Boiss. Uçucu Yağlarının Kimyasal Bileşimi ve Siklooksijenaz (COX) İnhibitör Aktivitelerindeki Fenolojik Evreye Bağlı Değişimler

## ÖZET

Bu çalışmada, *Origanum dubium* bitkisinin farklı gelişim evrelerindeki esansiyel yağ verimi, kimyasal bileşimi ve COX-1/2 inhibitör aktivitesi incelenmiştir. Uçucu yağ verimi %5.53 den %8.37 ye yükselmiş ve en yüksek verim çiçeklenme sonrası dönemde gözlemlenmiştir. GC-MS/FID analizleriyle, yağın başlıca bileşeninin karvakrol olduğu ve bitkinin gelişimi sırasında miktarının %64.4 den %86.9 a arttığı belirlenmiştir. Uçucu yağların COX-1/2 inhibitör aktiviteleri, ibuprofen ile karşılaştırmalı olarak değerlendirilmiştir. İbuprofenin inhibisyon oranı %73.53 olarak bulunurken, uçucu yağlar, vejetatif dönemde %52.13, çiçeklenme evresinde ise %57.76 oranında orta düzeyde inhibisyon göstermiştir. Çiçeklenme sonrası evrede inhibitör etki %68.16 ya yükselmiştir. Sonuçlar, karvakrol konsantrasyonundaki artışın COX-1/2 inhibitör aktivitesini güçlendirdiğini ve *O. dubium* esansiyel yağının doğal antiinflamatuar ajan olarak potansiyel taşıdığını göstermektedir.

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## INTRODUCTION

*Origanum dubium* Boiss., a wild oregano species native to Türkiye, holds significant commercial value. It is also found in the floras of Greece and Cyprus. A key characteristic of this species is its high essential oil yield, typically ranging from 6 to 8%. In Türkiye, *O. dubium* is predominantly wild-harvested along the Mediterranean coast (Turgut et al., 2017). *O. dubium* is being used traditionally both as an appetizer and a remedy for a variety of

health issues. These include gastrointestinal conditions like diarrhea, stomach pain, indigestion, and issues with the liver and gallbladder, as well as respiratory problems such as asthma, coughs, the common cold, and bronchitis. Additionally, it has been used to alleviate headaches, toothaches, and flu symptoms (Karousou & Deirmentzoglou, 2011).

Taxonomic ambiguities have been noted between *O. dubium* and *O. majorana*, particularly concerning their chemical profiles. Genomic and enzymatic pathway analyses suggest that *O. dubium* primarily follows the "cymyl pathway," which leads to the accumulation of key compounds such as γ-terpinene, p-cymene, along with their phenolic variants of carvacrol and thymol. In contrast, *O. majorana* predominantly utilizes the "sabinyl pathway," resulting in the production of sabinene and cis-trans sabinene hydrates. However, further studies on Turkish populations of *O. dubium* have indicated the existence of a "linalool pathway," which is characterized by the absence of cymyl and sabinyl compounds, presenting an additional layer of complexity to the species' metabolic pathways (Lukas et al., 2010; Lukas et al., 2013; Demirbolat et al., 2024)

Several chemotypes of *O. dubium* have been identified, including those exhibiting high concentrations of carvacrol (ranging from 72.7% to 86.2%), high linalool (ranging from 97.4% to 75.2%), and a carvacrol-linalool chemotype with carvacrol concentrations ranging from 35.3% to 62.9%, and linalool concentrations ranging from 27.8% to 58.6% (Figuérédo et al., 2006; Demirbolat et al., 2024). Most of the literature on *O. dubium* essential oils focuses primarily on the carvacrol chemotype (Arnold et al., 1993; Başer et al., 1993; Basim et al., 2019; Karioti et al., 2006; Turgut et al., 2017; Kaplan et al., 2019; Türkmen et al., 2022). Additionally, a previous study identified a chemotype characterized by linalool (35.5%) and 1,8-cineole (32.3%) as the major constituents (Souleles, 1991).

Inflammation constitutes a multifaceted physiological response orchestrated by the immune system, triggered by a variety of exogenous and endogenous stimuli, such as pathogenic microorganisms, cellular injury, and the presence of toxic substances. These stimuli can elicit both acute and chronic inflammatory responses, which are distinguished by unique cellular and molecular pathways (Chen et al., 2017). Among the central mediators of the inflammatory process are cyclooxygenase enzymes, specifically COX-1 and COX-2, which catalyze the conversion of arachidonic acid to prostaglandins and other bioactive lipid mediators. These mediators play integral roles in a wide array of physiological functions and pathological conditions, including the modulation of inflammation (Choi et al., 2009). Nonsteroidal anti-inflammatory drugs (NSAIDs), antioxidants, phytochemicals, and essential oils have been identified as potent inhibitors of COX enzymes. Through the suppression of COX activity, these agents diminish the synthesis of proinflammatory prostaglandins, thereby attenuating inflammatory responses and mitigating associated symptoms.

Plant physiology experiences dynamic alterations during its developmental stages, which subsequently impact a range of biochemical and physiological processes. These changes are expected to influence the biosynthesis of key volatile compounds, including essential oil constituents. This study presents a novel investigation into the influence of developmental stage-specific physiological changes on the essential oil composition of *O. dubium* and their corresponding cyclooxygenase (COX) inhibitory activity. To date, no comprehensive analysis has addressed the dynamic variation in volatile profiles across developmental phases in this species, nor their potential pharmacological implications. This research thus provides new insights into the intersection of plant developmental biology, secondary metabolism, and bioactivity.

## MATERIALS and METHODS

### Collection of plant materials and isolating essential oils

Cultivated specimens of *O. dubium* were harvested at different phenological stages between April and June from a single population maintained at the Aegean Agricultural Research Institute, Ministry of Agriculture and Forestry (Menemen, İzmir, Türkiye). Voucher specimens were deposited in the Aegean Agricultural Research Institute herbarium with the following number TR-77670. After collection, plant stems were separated, and the remaining aerial parts were subjected to air drying under ambient conditions. For essential oil extraction, 250 g of the dried aerial material was hydrodistilled in triplicate for 3 hours using a Clevenger-type apparatus. The recovered essential oils were dehydrated using anhydrous sodium sulfate and stored in amber glass vials at 4 $^0$C until further analysis.

### Analysis of essential oils

Gas chromatography coupled with flame ionization and mass spectrometric detection (GC-FID/MS) was employed for the analysis of essential oils using an Agilent system (Santa Clara, CA, USA). The system consisted of an Agilent 7890B gas chromatograph interfaced with an Agilent 5977E mass selective detector (MSD) via a capillary column splitter. Essential oil samples were diluted to 10% (v/v) in *n*-hexane, and 1 µL of each solution was injected using an Agilent G4513A autosampler. A HP-5MS capillary column (60 m × 0.25 mm i.d., 0.25 µm film thickness)

was employed for the analysis. The oven temperature was initially held at 60 $^0$C for 5 minutes, then increased to 200$^0$C at a rate of 3 $^0$C /min. Subsequently, the temperature was maintained isothermally for 5 minutes. Helium was employed as the carrier gas at a constant flow rate of 1.5 mL/min with a split ratio of 1:50. The temperatures of the injector port, MSD transfer line, ion source, quadrupole, and flame ionization detector (FID) were set to 250 $^0$C, 250 $^0$C, 230 $^0$C, 150 $^0$C, and 220 $^0$C, respectively. FID gas flows were adjusted to 400 mL/min for dry air and 30 mL/min for hydrogen. Mass spectra were recorded over the m/z range of 45 to 450. Compound identification was achieved by comparing the obtained mass spectra with those in the NIST 11 Mass Spectral Library (NIST11/2011/EPA/NIH). Retention indices (RIs) were calculated using a homologous series of *n*-alkanes ($C_7$–$C_{30}$) under identical chromatographic conditions and were subsequently compared with values reported in the NIST Chemistry WebBook. Quantitative analysis was performed by calculating the relative percentage of each compound based on its flame ionization detector peak area in relation to the total peak area of all detected components.

### Cyclooxygenase (COX) inhibition assays

Initially, the selectivity of the essential oils on COX-1 and COX-2 enzymes was assessed. Given the absence of selectivity, the inhibitory effects on the COX-1/2 enzyme mixture (1:1) were investigated. The inhibitory effects on cyclooxygenase (COX) enzymes were evaluated using a COX (ovine COX-1/human COX-2) inhibitor screening assay kit (Cayman Chemical, Ann Arbor, MI, USA), based on enzyme immunoassay methodology. The assay was conducted using an equal mixture of COX-1 and COX-2 enzymes. As per the kit instructions, a 100 µM concentration of the positive control ibuprofen (20.6 mg/L) and the test samples (equivalent to 20.6 mg/L or 100 µM ibuprofen) were incubated with the COX-1/2 enzyme mixture at 37 $^0$C for 10 minutes. The reaction was initiated by the addition of 10 µL of arachidonic acid (2 mM) as the substrate. After a 2-minute incubation at 37 $^0$C, the enzymatic reaction was terminated by the addition of 30 µL of saturated stannous chloride in hydrochloric acid, which facilitated the conversion of prostaglandin $H_2$ ($PGH_2$) to prostaglandin $F_2\alpha$ ($PGF_2\alpha$). The reaction mixture was then incubated at room temperature for 5 minutes. The resulting $PGF_2\alpha$ was quantified using ELISA, following the manufacturer's protocol. Absorbance was measured with an Epoch Absorbance Microplate Reader (BioTek Instruments, Inc., Winooski, VT, USA). All assays were performed in triplicate, and the inhibitory activity of the test compounds was expressed as the percentage inhibition of COX-1/2 enzymes at a concentration equivalent to 100 µM ibuprofen.

### Statistical analysis

All analyses were conducted in triplicate, and data are presented as mean (*M*) and standard deviation (*SD*). Comparisons between groups were made using one-way analysis of variance (ANOVA), followed by Tukey's Honestly Significant Difference (HSD) post hoc test, based on the homogeneity of sample sizes across groups. A significance level of $\alpha = 0.05$ was applied. Statistical analysis was performed using GraphPad Prism version 8.4.0 (GraphPad Software, San Diego, CA, USA).

## RESULTS and DISCUSSION

### Essential oil yields and compositions

Cultivated *O. dubium* yielded variable amounts of essential oils during plant development, as seen in Table 1. Values were presented as *M* and *SD*. Consistent with our results, yields of 5-14% were previously reported in Turkey (Turgut et al., 2017; Kaplan et al., 2019; Maral & Kırıcı, 2022). Essential oil yields were found to be significantly different between all phenological stages and tend to increase parallel to plant development. The highest yield was achieved at post post-flowering stage.

Table 1. Essential oil yields of *Origanum dubium* during plant growth.
*Çizelge 1. Gelişim evrelerine göre Origanum dubium uçucu yağ verimleri.*

| Stage of Growth | Collection Date | % Yield (ml 100 grams) |
|---|---|---|
| Before Flowering (BF) | 05.04.2025 | $M = 5.53$, $SD = 0.15^a$ |
| Initial Flowering (IF) | 13.05.2025 | $M = 7.63$, $SD = 0.25^a$ |
| Post Flowering (PF) | 27.06.2025 | $M = 8.37$, $SD = 0.15^a$ |

The values which are followed by the same letter in the same column are significantly different. [$F(2, 6) = 176.9$, $p < .001$, $\eta^2 = .98$]

### Composition of essential oils during plant development

Table 2 presents the chemical compositions of *O. dubium* essential oils collected at various phenological stages. Across all stages, the oils were predominantly composed of oxygenated monoterpenes, with carvacrol being the most abundant. Notably, the concentration of carvacrol increased significantly during plant development, rising from 64.4% to 86.9%. Conversely, γ-terpinene -an essential intermediate in the biosynthesis of carvacrol and thymol- showed a marked reduction, dropping from 15.4% to just 1.7% (Rudolph et al., 2016; Gago et al., 2025). Additionally, linalool became undetectable during and following the flowering stage.

Table 2. Essential oil compositions of *Origanum dubium* during plant growth.
*Çizelge 2. Gelişim evrelerine göre Origanum dubium uçucu yağ kompozisyonları.*

| | | | | | Composition (%) | | |
|---|---|---|---|---|---|---|---|
| No | Compounds | R.T | R.I$^{L}$ | R.I$^{C}$ | BF | IF | PF |
| 1 | Methyl 2-Methylbutanoate | 7.888 | 780 | 778 | N.D | 0.043 | N.D |
| 2 | α-Thujene | 13.890 | 927 | 926 | 0.917 | 1.356 | 1.474 |
| 3 | α-Pinene | 14.257 | 936 | 934 | 0.465 | 0.511 | 0.465 |
| 4 | Camphene | 15.006 | 950 | 955 | 0.068 | 0.091 | 0.105 |
| 5 | Sabinene | 16.179 | 973 | 972 | 1.078 | 0.109 | 0.071 |
| 6 | 1-Octen-3-ol | 16.300 | 975 | 976 | 0.196 | 0.086 | 0.131 |
| 7 | ß-Pinene | 16.381 | 978 | 981 | 0.233 | 0.176 | 0.164 |
| 8 | Myrcene | 16.941 | 989 | 987 | 1.420 | 1.656 | 1.459 |
| 9 | α-Phellandrene | 17.705 | 1004 | 1001 | 0.257 | 0.204 | 0.197 |
| 10 | Delta-3-Carene | 18.006 | 1007 | 1012 | 0.049 | 0.073 | 0.076 |
| 11 | α-Terpinene | 18.331 | 1017 | 1020 | 1.887 | 1.153 | 0.652 |
| 12 | p-Cymene | 18.737 | 1024 | 1022 | 2.465 | 2.757 | 2.880 |
| 13 | Limonene | 18.940 | 1025 | 1024 | 0.214 | 0.162 | 0.142 |
| 14 | ß-Phellandrene | 18.992 | 1027 | 1028 | 0.502 | 0.231 | 0.208 |
| 15 | 1,8-Cineole | 19.102 | 1031 | 1030 | 0.174 | 0.063 | 0.046 |
| 16 | cis-Ocimene | 19.281 | 1039 | 1041 | 0.168 | 0.051 | N.D |
| 17 | trans-Ocimene | 19.828 | 1054 | 1056 | 0.053 | 0.047 | N.D |
| 18 | Gamma-Terpinene | 20.494 | 1059 | 1062 | 15.462 | 4.701 | 1.712 |
| 19 | trans-Sabinenehydrate | 20.901 | 1066 | 1069 | 1.235 | 0.467 | 0.73 |
| 20 | α-Terpinolene | 21.958 | 1086 | 1089 | 0.472 | 0.127 | 0.079 |
| 21 | cis-Sabinenehydrate | 22.491 | 1099 | 1096 | 3.337 | 0.985 | 0.315 |
| 22 | Linalool | 22.577 | 1100 | 1103 | 7.181 | N.D | N.D |
| 23 | 1-Octen-3-yl-Acetate | 22.960 | 1119 | 1117 | 0.047 | 0.063 | N.D |
| 24 | 1-Terpineol | 23.647 | 1136 | 1131 | 0.228 | N.D | 0.038 |
| 25 | Pinocarveol | 24.531 | 1143 | 1145 | 0.113 | N.D | N.D |
| 26 | Borneol | 25.897 | 1166 | 1171 | 0.205 | 0.238 | 0.367 |
| 27 | 4-Terpineol | 26.488 | 1177 | 1179 | 3.915 | 0.811 | 0.381 |
| 28 | α-Terpineol | 27.062 | 1190 | 1189 | 0.487 | 0.017 | 0.058 |
| 29 | Carvone | 29.960 | 1243 | 1249 | 0.289 | 0.155 | 0.130 |
| 30 | Linalyl Acetate | 30.204 | 1253 | 1255 | 0.171 | 0.151 | N.D |
| 31 | Thymol | 31.650 | 1302 | 1301 | 0.359 | 0.388 | 0.395 |
| 32 | Carvacrol | 32.461 | 1317 | 1322 | 64.420 | 81.670 | 86.911 |
| 33 | Neryl Acetate | 35.696 | 1363 | 1367 | 0.052 | 0.069 | N.D |
| 34 | Caryophyllene | 37.685 | 1420 | 1425 | 0.681 | 0.562 | 0.336 |
| 35 | ß-Copaene | 40.226 | 1436 | 1433 | 0.081 | 0.047 | 0.037 |
| 36 | α-Humulene | 40.860 | 1452 | 4163 | 0.130 | 0.131 | 0.084 |
| 37 | Spathulenol | 44.106 | 1577 | 1572 | 0.081 | 0.081 | 0.179 |
| Total Identified (%) | | | | | 99.092 | 99.432 | 99.822 |
| Oxygenated Hydrocarbons (1, 6, 23) | | | | | 0.243 | 0.192 | 0.131 |
| Monoterpene Hydrocarbons (2-5, 7-14, 16-18, 20) | | | | | 15.710 | 13.405 | 9.684 |
| Oxygenated Monoterpenes (15, 19, 21, 22, 24-33) | | | | | 82.166 | 85.014 | 89.371 |
| Sesquiterpene Hydrocarbons (34-36) | | | | | 0.892 | 0.740 | 0.457 |
| Oxygenated Sesquiterpenes (37) | | | | | 0.081 | 0.081 | 0.179 |

R.T; Retention time, R.I$^{L}$; retention index from NIST webbook, R.I$^{C}$; calculated retention index, BF; before flowering, IF; initial flowering, PF; post flowering, N.D; not detected. Results were presented as mean values of 3 analyses.

### COX inhibitions

Existing literature does not report the antiinflammatory activity of *O. dubium* essential oil. However, a previous study demonstrated that *O. minutiflorum*, which possesses a similar essential oil composition, exhibited cyclooxygenase (COX) inhibitory activity. Specifically, *O. minutiflorum* inhibited COX-1 by 55.26% at a concentration of 100 µg/mL (Yıldız et al., 2023). The COX-1/2 inhibitory activities of *Origanum dubium* essential oil, with ibuprofen serving as the positive control, are presented in Table 3 as *M* and *SD*. Ibuprofen, a non-selective COX inhibitor, exhibited a 73.53% inhibition rate against a COX-1/2 enzyme mixture. Comparatively, the essential oil derived from *O. dubium* exhibited markedly lower COX inhibitory activity during the vegetative (52.13%) and initial flowering (57.76%) stages. However, at the post-flowering stage, its inhibitory efficacy increased substantially to 68.16%, approaching the level of inhibition observed with the standard anti-inflammatory drug ibuprofen. Although no statistically significant difference was observed between the BF and IF stages, all other pairwise comparisons revealed significant differences.

Table 3. COX-1/2 activities of ibuprofen and essential oils.
*Çizelge 3. Uçucu yağlar ve ibuprofenin COX-1/2 aktiviteleri.*

| Sample | COX-1/2 inhibition (%) |
|---|---|
| *O.dubium* essential oil before flowering (BF) | $M = 52.13$, $SD = 3.79^{a}$ |
| *O. dubium* essential oil initial flowering (IF) | $M = 57.76$, $SD = 2.46^{b}$ |
| *O. dubium* essential oil post flowering (PF) | $M = 68.16$, $SD = 3.21^{a,b}$ |
| Ibuprofen | $M = 73.53$, $SD = 3.61^{a,b}$ |

The values which are followed by the same letter in the same column are significantly different. [$F(3, 8) = 25.88$, $p < .001$, $\eta^2 = .91$]

The essential oil of *O. dubium* is primarily composed of oxygenated monoterpenes, with carvacrol identified as the predominant component. The presence of a hydroxyl group in carvacrol allows it to function as both a hydrogen bond donor and acceptor, potentially enhancing its binding affinity to enzymes' active sites through hydrogen bonding. Furthermore, the aromatic ring of carvacrol facilitates π-π stacking interactions, similar to those formed by the phenyl moiety of ibuprofen, thereby contributing to its bioactivity. The isobutyl side chain of ibuprofen bears structural similarity to the isopropyl group of carvacrol, with both moieties contributing to hydrophobic interactions within the enzyme's active site. These interactions likely play a key role in enhancing the binding affinity of both compounds. Increasing the concentration of carvacrol enhances the COX-1/2 inhibitory potential of *O. dubium* essential oils.

## CONCLUSION

This study demonstrates that both the yield and composition of essential oils in *O. dubium* vary significantly across phenological stages. The highest oil yields and biological activity were observed in the post-flowering stage, coinciding with a marked increase in carvacrol concentration. Carvacrol, the dominant oxygenated monoterpene identified, likely underpins the essential oil's COX-1/2 inhibitory activity due to its structural and functional resemblance to ibuprofen. Although the essential oil exhibited limited COX inhibition during early developmental stages, its post-flowering extract showed inhibition levels comparable to ibuprofen. These results indicate a strong correlation between carvacrol content and anti-inflammatory potential, marking the first report of such bioactivity in *O. dubium*. Overall, the findings support further pharmacological investigation into *O. dubium* as a promising natural source of plant-based COX inhibitors.

### Conflict of Interest

The author declares no conflict of interest.

## REFERENCES

Arnold, N., Bellomaria, B., Valentini, G., & Arnold, H. J. (1993). Comparative study of the essential oils from three species of origanum growing wild in the eastern Mediterranean region. *Journal of Essential Oil Research*, *5*(1), 71–77. https://doi.org/10.1080/10412905.1993.9698172

Başer, K. H. C., Kirimer, N., & Tümen, G. (1993). Composition of the essential oil of *Origanum majorana* L. from Turkey. *Journal of Essential Oil Research*, *5*(5), 577–579. https://doi.org/10.1080/10412905.1993.9698283

Basim, H., Turgut, K., Kaplan, B., Basim, E., & Turgut, A. (2019). The potential application of *Origanum dubium* Boiss. Essential oil as a seed protectant against bean and tomato seed-borne bacterial pathogens. *Acta Scientiarum Polonorum Hortorum Cultus*, *18*(3), 79–86. https://doi.org/10.24326/asphc.2019.3.8

Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X., & Zhao, L. (2017). Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*, *9*(6), 7204. https://doi.org/10.18632/oncotarget.23208

Choi, S. H., Aid, S., & Bosetti, F. (2009). The distinct roles of cyclooxygenase-1 and neuroinflammation: Implications for translational research. *Trends in Pharmacological Sciences*, *30*(4), 174–181. https://doi.org/10.1016/j.tips.2009.01.002

Demirbolat, İ., Karik, Ü., & İşcan, İ. (2024). Effect of cultivation and geographical location on chemical composition and enantiomeric distribution in linalool-rich *Origanum dubium* Boiss. essential oils obtained at different growth stages. *Journal of Essential Oil Research*, *37*(1), 88–94. https://doi.org/10.1080/10412905.2024.2404085

Figuérédo, G., Cabassu, P., Chalchat, J. C., & Pasquier, B. (2006). Studies of Mediterranean oregano populations. VII: Chemical composition of essential oils of carvacrol-rich oregano of various origins. *Journal of Essential Oil Research*, *18*(3), 244–249. https://doi.org/10.1080/10412905.2006.9699077

Gago, C., Serralheiro, A., & Miguel, M. D. G. (2025). Anti-inflammatory activity of thymol and thymol-rich essential oils: mechanisms, applications, and recent findings. *Molecules, 30*(11), 2450. https://doi.org/10.3390/molecules30112450

Kaplan, B., Sözmen, E. U., & Turgut, K. (2019). Chemical diversity of essential oils within the population of *Origanum dubium* Boiss. *Natural Volatiles and Essential Oils*, *6*(4), 6–12.

Karioti, A., Vrahimi-Hadjilouca, T., Droushiotis, D., Rancic, A., Hadjipavlou-Litina, D., & Skaltsa, H. (2006). Analysis of the essential oil of *Origanum dubium* growing wild in Cyprus. Investigation of its antioxidant capacity and antimicrobial activity. *Planta Medica*, *72*(14), 1330–1334. https://doi.org/10.1055/s-2006-947255

Karousou, R., & Deirmentzoglou, S. (2011). The herbal market of Cyprus: Traditional links and cultural exchanges. *Journal of Ethnopharmacology, 133*(1), 191-203. https://doi.org/10.1016/j.jep.2010.09.034

Lukas, B., Samuel, R., & Novak, J. (2010). Oregano or marjoram? The enzyme γ-terpinene synthase affects chemotype formation in the genus Origanum. *Israel Journal of Plant Sciences*, *58*(3-4), 211–220. https://doi.org/10.1560/ IJPS.58.3-4.211

Lukas, B., Samuel, R., Mader, E., Başer, K. H. C., Duman, H., & Novak, J. (2013). Complex evolutionary relationships in Origanum section Majorana (Lamiaceae). *Botanical Journal of the Linnean Society*, *171*(4), 667–686. https://doi.org/10.1111/boj.12022

Maral, H., & Kırıcı, S. (2022). Farklı ekolojik koşullarda yetiştirilen *Origanum dubium* Boiss'in bazı verim ve kalite özelliklerinin belirlenmesi. *KSÜ Tarım ve Doğa Dergisi*, *25*(6), 1434–1447. https://doi.org/10.18016/ksutarimdoga.vi.910746

Rudolph, K., Parthier, C., Egerer-Sieber, C., Geiger, D., Müller, Y. A., Kreis, W., & Müller-Uri, F. (2016). Expression, crystallization, and structure elucidation of γ-terpinene synthase from Thymus vulgaris. *Acta Crystallographica Section F: Structural Biology Communications*, *72*(1), 16–23. https://doi.org/10.1107/s2053230x15023043

Souleles, C. (1991). Volatile constituents of *Origanum dubium* leaves and stem - bark. *Planta Medica*, *57*(01), 77–78. https://doi.org/10.1055/s-2006-960024

Turgut, K., Ozyigit, Y., Tutuncu, B., & Sonmez, E. U. (2017). Agronomic and chemical performance of selected *Origanum dubium* Boiss. clones for industrial use. *Turkish Journal of Agriculture and Forestry*, *41*(4), 272–277. https://doi.org/10.3906/tar-1612-75

Türkmen, M., Kara, M., Maral, H., & Soylu, S. (2022). Determination of the chemical component of the essential oil of *Origanum dubium* plants grown at different altitudes and antifungal activity against Sclerotinia sclerotiorum. *Journal of Food Processing and Preservation*, *46*(6), e15787. https://doi.org/10.1111/jfpp.15787

Yıldız, G., Demirci, B., Temel, H. E., & Kırımer, N. (2023). *Origanum minutiflorum* O. Schwarz et PH Davis essential oil: Enzyme inhibitory activities and chemical composition. *Journal of Research in Pharmacy, 27*(5), 2160–2169. https://dx.doi.org/10.29228/jrp.498