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Variations in Essential Oil Compositions and Cyclooxygenase (COX) Inhibiting Potential of *Ruta chalepensis* L. Essential Oils Obtained at Different Phenological Stages

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ABSTRACT

This study examines the yield, composition, and COX inhibitory activity of essential oils from *Ruta chalepensis* L. obtained at various developmental stages. Essential oil yield decreased with plant maturity, reaching its lowest level during the post-flowering stage. Chemical analysis revealed the absence of terpenes, with notable shifts in aliphatic ketones. At the vegetative stage, 2-nonanone was dominant (58%), but declined to 26% in mature plants. In contrast, 2-undecanone increased from 34% to 63%, indicating a developmental shift in longer chain molecule biosynthesis. COX-1/2 inhibition assays showed that ibuprofen inhibited enzyme activity by 73.53%, whereas *R. chalepensis* essential oils exhibited significantly lower inhibition, suggesting weak anti-inflammatory activity. These results indicate that the essential oil does not account for the plant's anti-inflammatory traditional medicinal use, and other constituents may be responsible for its therapeutic effects.

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Farklı Fenolojik Evrelerde Elde Edilen *Ruta chalepensis* L. Uçucu Yağlarının Kimyasal Kompozisyonları ve Siklooksijenaz (COX) İnhibisyon Potansiyellerindeki Değişiklikler

ÖZET

Bu çalışma, farklı gelişim aşamalarında elde edilen *Ruta chalepensis* L. uçucu yağlarının verimi, bileşimi ve COX inhibitör aktivitesini incelemektedir. Uçucu yağ verimi, bitkinin olgunlaşmasıyla azalmış ve en düşük seviye çiçeklenme sonrası dönemde gözlemlenmiştir. Kimyasal analizler terpen bileşenleri içermediğini ortaya koymuş ve alifatik ketonlarda belirgin değişimler görülmüştür. Vejetatif dönemde 2-nonanone baskın olup (%58), olgun bitkilerde bu oran 26%'ya düşmüştür. Buna karşılık, 2-undecanone oranı 34%'ten 63%'e yükselmiştir. Bu sonuçlar daha uzun zincirli molekül biyosentezinde gelişimsel bir değişimi göstermektedir. COX-1/2 inhibitör testleri, ibuprofenin enzim aktivitesini 73,53% oranında engellediğini gösterirken, *R. chalepensis* uçucu yağları belirgin şekilde daha düşük inhibitör aktivite sergilemiştir. Bu sonuçlar, uçucu yağın bitkinin geleneksel anti-inflamatuar tıbbi kullanımından sorumlu olmadığını ve terapötik etkilerinin diğer bileşenlerden kaynaklanabileceğini göstermektedir.

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INTRODUCTION

Fringed rue (*Ruta chalepensis* L.), known locally as sedef otu in Türkiye, is a perennial herbaceous species belongs to the *Rutaceae* family, widely distributed throughout the Mediterranean region (Yaman et al., 2019). The plant can grow up to 80 cm in height. Its blue-green, pale leaves are bipinnatisect and compound, comprising multiple

segments that further subdivide into smaller leaflets. The inflorescence consists of clusters of bright yellow flowers, each bearing four to five petals. The fruit is characterized by a rough capsule with pointed lobes (Iauk et al., 2004).

Ruta chalepensis has a long history of use in traditional herbal medicine across various cultures for the treatment of rheumatism, fever, and neurological disorders such as convulsions. It is also utilized for its analgesic and antipyretic properties (Al-Said et al., 1990; Iauk et al., 2004). Additionally, the plant has been reported to exhibit abortifacient, emmenagogue, anthelmintic, spasmolytic, and anti-inflammatory activities. Pharmacologically, it acts as a central nervous system depressant (Di Stasi et al., 2002; Gonzalez-Trujano et al., 2006; Khlifi et al., 2013). In Türkiye, oral administration of 1–5 drops of *R. chalepensis* essential oil is traditionally employed as a sedative and is also used to alleviate flatulence (Baytop, 1999).

The essential oil of *Ruta chalepensis* is a clear yellow liquid characterized by an unpleasant, pungent odor. Unlike many essential oils that are predominantly composed of terpenes, *R. chalepensis* essential oil is terpeneless and primarily consists of long-chain aliphatic ketones, notably 2-nonanone and 2-undecanone. The major constituents of essential oils from various *Ruta* species across different geographical regions have been extensively documented (Nahar et al., 2021). Furthermore, essential oils from *Ruta* spp. have demonstrated a wide spectrum of biological activities, including antimicrobial, antifungal, antibacterial, antioxidant, anti-inflammatory, antiparasitic, cytotoxic, herbicidal, insecticidal, insect repellent, larvicidal, nematocidal, and antihelmintic effects (Nahar et al., 2021). However, these investigations have typically focused on a single phenological stage, predominantly post-flowering, with limited studies addressing variations across other growth stages.

Inflammation represents a complex biological response of the immune system, initiated by diverse stimuli including pathogenic microorganisms, cellular damage, and exposure to toxic agents. These stimuli can provoke both acute and chronic inflammatory processes, characterized by distinct cellular and molecular mechanisms (Chen et al., 2017). Cyclooxygenase enzymes, COX-1 and COX-2, serve as the key rate-limiting enzymes catalyzing the conversion of arachidonic acid to prostaglandins and other lipid mediators, which play pivotal roles in various physiological and pathological processes, including the modulation of inflammatory responses (Choi et al., 2009). Nonsteroidal anti-inflammatory drugs (NSAIDs), antioxidants, plant extracts, and even essential oils have been found to inhibit COX enzymes, thereby attenuating the synthesis of proinflammatory prostaglandins and reducing inflammation.

Plant physiology undergoes dynamic changes throughout development, which in turn influence various biochemical and physiological processes. These alterations are also likely to affect the biosynthesis of essential oil constituents. Although *Ruta chalepensis* is widely recognized for its medicinal properties, the variation in its essential oil composition across different growth stages remains insufficiently characterized. This study aims to analyze the chemical profile of *Ruta chalepensis* essential oils at distinct developmental stages and evaluate their inhibitory effects on cyclooxygenase (COX) enzymes.

MATERIALS and METHODS

Collection of plant materials and isolating essential oils

Approximately 1 kg of cultivated *Ruta chalepensis* L. was collected from the same population at distinct growth stages between December and April from the Zeytinburnu Medicinal Plants Garden, Istanbul, Türkiye (GPS coordinates: 41°00'31.5"N, 28°54'59.0"E). Voucher specimens were previously deposited in the Zeytinburnu Medicinal Plants Garden herbarium with the catalog number of 000221. Fresh aerial parts were subjected to hydrodistillation for 3 hours in triplicate using a Clevenger-type apparatus. The extracted essential oils were subsequently dried over anhydrous sodium sulfate (Na_2SO_4) and stored in amber vials at 4°C until further chemical analysis.

Analysis of essential oils

Essential oil analysis was conducted using an Agilent GC-FID/MS system (Santa Clara, CA, USA), comprising an Agilent 7890B gas chromatograph coupled with an Agilent 5977E mass selective detector via a capillary column splitter. Essential oil samples were prepared as 10% (v/v) solutions in n-hexane, and 1 µL aliquots were injected using an Agilent G4513A autosampler. Separation was achieved on a DB-WAX capillary column (60 m × 0.25 mm i.d., 0.25 µm film thickness) under the following temperature program: initial isothermal hold at 70°C for 15 minutes; ramped to 180°C at 2°C/min and held for 5 minutes; subsequently increased to 230°C at 5°C/min and maintained isothermally for 15 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°C, 250°C, 230°C, 150°C, and 220°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.

Identification of compounds was performed by comparing their spectral data with the NIST 11 Mass Spectral Library (NIST11/2011/EPA/NIH). C7-C30 homologous alkane series were used to evaluate retention indices and were later compared with NIST online webbook data. Quantification was carried out by calculating the percentage of FID responses for each compound detected.

Cyclooxygenase (COX) inhibition assays

The inhibitory effects on COX enzyme activity were evaluated using a COX (ovine/human) Inhibitor Screening Assay Kit (Cayman Chemical, Ann Arbor, MI, USA), which employs an enzyme immunoassay-based method. 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. According to the kit's protocol, both the positive control (ibuprofen at 100 µM, equivalent to 20.6 mg/L) and the essential oils (also at 20.6 mg/L to match 100 µM ibuprofen equivalence) were incubated with the COX-1/2 enzyme mixture for 10 minutes at 37°C. The enzymatic reaction was then initiated by adding 10 µL of arachidonic acid (2 mM) as the substrate. Following a 2-minute incubation at 37°C, the reaction was stopped by adding 30 µL of saturated stannous chloride in hydrochloric acid, which converts prostaglandin H2 (PGH2) to prostaglandin F2α (PGF2α). The reaction mixture was then left at room temperature for 5 minutes. PGF2α levels were quantified using ELISA as per the manufacturer's instructions, and absorbance was measured using an Epoch Absorbance Microplate Reader (BioTek Instruments, Inc., Winooski, VT, USA). All experiments were performed in triplicate, and the inhibitory activity of the test compounds was expressed as the percentage inhibition of COX-1/2 activity at the 100 µM ibuprofen-equivalent concentration (Demirbolat et al., 2022).

Statistical analysis

All analyses were performed in triplicate. Descriptive statistics were given as mean ± standard deviation (SD). The comparisons were conducted using one-way ANOVA, followed by Tukey's Honestly Significant Difference (HSD) post hoc test, due to the homogeneity of sample sizes across the groups. The level of significance was taken as $\alpha=0.05$. Statistical analysis was performed using GraphPad Prism 8.4.0 (GraphPad Software, San Diego, CA, USA).

RESULTS and DISCUSSION

Essential oil yields

Cultivated *R. chalepensis* yielded variable amounts of essential oils, as seen in Table 1. Values were presented as mean ± SD. Essential oil yields decreased during the plant development, especially in the post-flowering stage. Yields were previously reported as 1.13% (w/w) in Iran, 0.16% (v/w) in Türkiye, 0.2% (v/w) in India, and 0.39% (v/w) in Tunisia (Bagchi et al., 2003; Baser et al., 1996; Ncibi et al., 2020; Rustaiyan et al., 2002). Nahar et al. (2021) reviewed the essential oil yields of *Ruta chalepensis* across various geographical regions and plant parts used. Literature reports indicate that the oil yield is influenced by the plant part distilled and the geographic origin of the species.

Table 1. Essential oil yields of *Ruta chalepensis* L. during plant growth.
Çizelge 1. Ruta chalepensis L. bitkisinin büyüme sürecinde uçucu yağ verimi.

Stage of Growth	Collection Date	% Yield (ml 100 grams)
Before Flowering (BF)	10.12.2024	0.48 ± 0.07[a]
Initial Flowering (IF)	14.02.2025	0.41 ± 0.06
Post Flowering (PF)	18.04.2025	0.31 ± 0.02[a]

The values followed by the same letter in the same column are significantly different. [$F(2, 6) = 5.761$, $p < .05$]

Composition of essential oils during plant development

The chemical composition of *Ruta chalepensis* essential oils at various developmental stages is presented in Table 2. Notably, all samples were characterized by the absence of terpenes. The most significant compositional variations were observed in the concentrations of two aliphatic ketones: 2-nonanone and 2-undecanone. During the vegetative phase, 2-nonanone constituted approximately 58% of the essential oil, whereas its proportion declined markedly to 26% in the mature stage. In contrast, the relative abundance of 2-undecanone increased substantially from 34% during the vegetative stage to 63% at full maturity. This trend reflects a developmental shift favoring the biosynthesis of higher molecular weight aliphatic ketones, particularly those with longer carbon chains.

Consistent with these findings, studies conducted in Turkey at the full flowering stage also identified 2-undecanone and 2-nonanone as the principal constituents of *R. chalepensis* essential oil. Başer et al. (1996) reported

concentrations of 66.49% and 16.24% for 2-undecanone and 2-nonanone, respectively, while Ali et al. (2013) found 43.2% and 27.9%. By contrast, a study from Greece reported that essential oil extracted at plant maturity was characterized by a predominance of terpenes (Tzakou & Couladis, 2001).

According to Krayni et al. (2018), the essential oils extracted from the leaves and stems of *R. chalepensis* were primarily composed of 2-undecanone (23.0–37.7%) and 2-nonanone (16.7–23.0%). However, the essential oil obtained from the fruits contained higher proportions of these compounds, with 2-undecanone (57.5–58.4%) and 2-nonanone (19.0–23.3%).

Similarly, Tounsi et al. (2011) reported that among different plant organs, flowers (60.46%) and fruits (41.06%) exhibited the highest concentrations of 2-undecanone. Investigations on Tuisian populations of *R. chalepensis* have also confirmed the dominance of 2-undecanone. Akkari et al. (2015) showed that essential oils obtained during the full flowering stage contained 85.94% 2-undecanone in leaves and 89.89% in flowers. Similarly, Mejri et al. (2010) reported that dried leaves yielded 69.23% 2-undecanone, while dried flowers contained 100%. Najem et al. (2020) further demonstrated that essential oils extracted at the full flowering stage in Morocco contained 64% 2-undecanone and only 0.1% 2-nonanone, highlighting the predominance of 2-undecanone at this developmental stage, possibly due to its accumulation in the flowers and fruits. A phenological stage-dependent study conducted in India primarily focused on different organs of the plant during development and reported that 2-undecanone was dominant in flowers (67.8%) and fruits (60.0%) (Bagchi et al., 2003). The elevated concentration of 2-undecanone in the fruits and flowers may account for the observed increase of this compound in the full flowering stage.

A broader comparative study by Nahar et al. (2021), which summarized the major components of *R. chalepensis* essential oils from different geographical origins and plant parts distilled, confirmed that 2-undecanone was the predominant compound.

Table 2. Essential oil compositions of *Ruta chalepensis* L. during plant growth.
Çizelge 2. Ruta chalepensis L. bitkisinin büyüme dönemindeki uçucu yağ bileşimleri.

					Composition (%)		
No	Compounds	RT	RI^L	RI^C	BF	IF	PF
1	Isopropyl 2-methylbutanoate	6.352	1061	1065	0.062	0.081	0.049
2	Isopropyl 3-methylbutanoate	6.732	1083	1087	ND	ND	0.115
3	2-Heptanone	11.245	1185	1182	0.11	ND	0.374
4	2-Octanone	18.155	1297	1291	1.032	0.634	0.408
5	Geijerene	20.906	1338	1333	0.111	0.255	0.129
6	2-Nonanone	26.495	1413	1420	55.962	45.537	26.484
7	Octyl acetate	31.494	1476	1474	0.867	1.293	0.651
8	2-Decanone	33.606	1497	1493	3.943	3.447	3.607
9	2-Nonanol	35.697	1511	1516	0.384	0.584	0.409
10	Pregeijerene	38.057	1594	1591	1.219	2.072	1.292
11	2-Undecanone	40.863	1606	1613	34.332	42.593	62.508
12	2-Undecanol	44.572	1704	1707	0.127	0.16	0.204
13	2-Dodecanone	44.811	1709	1712	0.424	0.605	0.716
14	6-Dodecanone	46.867	1751	1756	0.487	0.647	0.873
15	6-Dodecanol	48.018	1782	1778	ND	0.111	0.256
16	2-Tridecanone	52.802	1816	1811	0.27	0.516	0.959
Percentage of Total Identified Compounds					99.33	98.535	99.034
Hydrocarbons (5, 10)							
Oxygenated Hydrocarbons (1-4, 6-9, 11-16)							

RT: retention time, RI^L: literature retention index, RI^C: calculated retention index, BF: before flowering, IF: initial flowering, PF: post flowering, ND: not detected. Results were presented as mean values of 3 analyses.

COX inhibitions

The anti-inflammatory effects of *Ruta chalepensis* essential oil have been previously investigated using the carrageenan-induced paw edema model in albino mice. This widely accepted experimental model allows for the assessment of acute inflammation and the efficacy of potential anti-inflammatory agents. The results from this study demonstrated that the essential oil of *R. chalepensis* exhibited significant anti-inflammatory activity, showing a level of efficacy comparable to that of the commonly used standard drug, diclofenac (Boudjema et al., 2018). This suggests that compounds present in the essential oil may modulate inflammatory pathways effectively. However, despite these promising results, there is a lack of literature specifically addressing the cyclooxygenase

(COX) inhibitory activity of *R. chalepensis* essential oil. The COX-1/2 inhibitory activities of the essential oils and ibuprofen are summarized in Table 3 as mean ± SD. As expected, ibuprofen exhibited a significant inhibitory effect on the COX enzyme mixture, achieving an inhibition rate of 73.53%, thereby confirming its potent anti-inflammatory mechanism. In contrast, *Ruta chalepensis* essential oils showed noticeably lower inhibitory activities against the COX enzymes, indicating a relatively reduced potency compared to ibuprofen.

Table 3. COX-1/2 activities of ibuprofen and essential oils.
Çizelge 3. İbuprofen ve uçucu yağların COX-1/2 aktiviteleri

Sample	COX-1/2 inhibition (%)
R. chalepensis essential oil before flowering (BF)	13.12 ± 3.82^{a}
R. chalepensis essential oil initial flowering (IF)	11.28 ± 2.58^{b}
R. chalepensis essential oil post flowering (PF)	7.86 ± 3.74^{c}
Ibuprofen	$73.53 \pm 3.61^{a,b,c}$

The values that are followed by the same letter in the same column are significantly different. [$F(3, 8) = 246.1$, $p < .05$]

Ruta chalepensis essential oils primarily consist of ketones containing saturated aliphatic hydrocarbon chains. The relatively low inhibitory activity observed in these oils may be attributed to the structural characteristics of these ketones. Since those ketonic structures generally lack enough heteroatoms or aromatic rings that could facilitate the formation of critical interactions with the active sites of enzymes. This structural limitation may explain the lower potency of *R. chalepensis* essential oils compared to ibuprofen, with more favorable functional groups for enzyme binding. Furthermore, no statistically significant differences were observed between the essential oils, making it impossible to determine whether 2-undecanone or 2-nonanone exhibits greater activity against cyclooxygenase enzymes. Antioxidant compounds are often effective in inhibiting COX isoenzymes. However, a previous study reported that *R. chalepensis* essential oil does not exhibit even moderate antioxidant activity, which may explain its relatively lower inhibitory effect on COX enzymes (Ahmet et al., 2011).

These findings suggest that while the essential oil does possess anti-inflammatory properties in vivo (Boudjema et al., 2018), its mechanism may not be primarily through COX inhibition.

CONCLUSION

This study holds considerable significance as it offers a comprehensive analysis of the essential oil yield and chemical composition of *Ruta chalepensis*, a plant renowned for its prominent medicinal properties, across various phenological stages. Additionally, the findings reveal that the anti-inflammatory effects commonly associated with *Ruta chalepensis* in traditional use cannot be ascribed to its essential oil. This indicates that the bioactive compounds responsible for this therapeutic effect may reside in other parts of the plant, suggesting that factors beyond the essential oil contribute to its medicinal efficacy.

Conflict of Interest

The author declares no conflict of interest.

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