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Quantitative analysis and antioxidant activity of *Trifolium pratense* L. stem

Trifolium pratense L. gövdesinin kantitatif analizi ve antioksidan aktivitesi

Ramazan Erenler[1, 2*], İlyas Yıldız[1], Esma Nur Geçer[2], İbrahim Hosaflıoğlu[1], Süleyman Muhammed Çelik[1]

[1]Iğdır University, Research Laboratory Practice and Research Center, 76000 Iğdır, Türkiye

[2]Tokat Gaziosmanpaşa University, Faculty of Arts and Sciences, Department of Chemistry, 60240 Tokat, Türkiye

ABSTRACT

The use of natural products for medical and nutritional purposes dates back to ancient times and has made significant contributions to the discovery and development of drugs, thanks to the compounds they contain. In this study, quantitative analysis of phenolic compounds and antioxidant activity of *Trifolium pratense* stem were determined. Rutin (0.075 mg/g extract), salicylic acid (0.044 mg/g extract), trans-ferulic acid (0.004 mg/g extract), gallic acid (0.003 mg/g extract), and hesperidin (0.024 mg/g extract) were determined as major compounds. The antioxidant activity of the methanol extract of the stem was evaluated using the DPPH and ABTS assays. In the DPPH assay, the extract exhibited moderate activity with an IC_{50} value of 17.22 ± 0.67 µg/mL. The activities of BHA and BHT were calculated as (5.47 ± 0.23, IC_{50}, µg/mL) and (10.67 ± 0.20, IC_{50}, µg/mL), respectively. Regarding the ABTS activity, the extract displayed high activity (IC_{50}, 9.03 ± 0.11 µg/mL). The standard BHT activity was detected as 9.51 ± 0.25 µg/mL (IC_{50}). *Trifolium pratense* stem could be a valuable source of antioxidant and bioactive compounds that can be isolated from the corresponding plants.

Keywords: *Trifolium pratense* L. stem, LC-MS/MS, antioxidant activity

ÖZET

Doğal ürünlerin tıbbi ve beslenme amaçlı kullanımı çok eski çağlara dayanmakta olup, içerdikleri bileşikler sayesinde ilaçların keşfi ve geliştirilmesine önemli katkılarda bulunmuştur. Bu çalışmada, *Trifolium pratense* gövdesinin fenolik bileşiklerinin kantitatif analizi ve antioksidan aktivitesi belirlenmiştir. Rutin (0,075 mg/g ekstre), salisilik asit (0,044), trans-ferulik asit (0,0385), gallik asit (0,0329) ve hesperidin (0,024) ana ürün olarak belirlenmiştir. Sapın metanol ekstresinin antioksidan aktivitesi DPPH ve ABTS analizleri kullanılarak değerlendirilmiştir. DPPH analizinde ekstre, 17,22 ± 0,67 µg/mL'lik bir IC_{50} değeriyle orta düzeyde aktivite göstermiştir. BHA ve BHT aktiviteleri sırasıyla (5.47 ± 0.23, IC_{50}, µg/mL) ve (10.67 ± 0.20, IC_{50}, µg/mL) olarak hesaplandı. ABTS aktivitesine gelince, ekstre yüksek aktivite gösterdi (IC_{50}, 9.03 ± 0.11 µg/mL). Standart BHT'nin aktivitesi 9.51 ± 0.25 µg/mL (IC_{50}) olarak tespit edildi. *Trifolium pratense* sapı, ilgili bitkilerden izole edilebilen değerli biyoaktif bileşik kaynağı ve antioksidan olabilir.

Anahtar kelimeler: *Trifolium pratense* L. gövde, LC-MS/MS, antioksidan aktivite

***Correspondence:**
rerenler@gmail.com

ORCID iD:
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Introduction

Human beings have been using plants as a source of nutrients for years (Cragg et al., 1997; Guemidi et al., 2024; Sahin Yaglioglu et al., 2013; Topçu et al., 1999). With the development of spectroscopy in the 19th century, the importance of plants increased considerably. Bioactive compounds in plants have been isolated by chromatographic methods, and their structures have been determined by spectroscopic techniques (Zerrouki et al., 2022). Bioactive compounds have been used in the pharmaceutical and food industries (Aksit et al., 2014; Bayir et al., 2014). Thus, active compounds in plants have become a valuable resource in the pharmaceutical industry (Erenler et al., 2014; Kaya et al., 2014; Türkmen et al., 2014). Intensive studies are being conducted on the synthesis of natural compounds. These studies include total synthesis, semi-synthesis, and functionalization of natural products (Lu et al., 2014). Synthetic chemists have taken inspiration from natural products and have begun to synthesize them (Çelik et al., 2007; Erenler et al., 2007; Erenler et al., 2006; Erenler et al., 2009). Thus, new drugs have been introduced, which are a turning point in drug discovery. Quantitative analysis of phenolics is crucial for various fields, including agriculture, medicine, and industry. Accurate measurement allows for better utilization of plant resources, improved health benefits, and enhanced product quality (Erenler, Demirtas, et al., 2018; Erenler, Telci, et al., 2018; Erenler et al., 2015; Genç et al., 2020). Phenolics help plants defend against pathogens, herbivores, and environmental stresses. They contribute to the regulation of growth and signaling pathways in plants. Determining the amount of phenolic compounds in a plant with a high concentration will allow the isolation of these compounds from the relevant plant. Phenolic compounds are plant-derived secondary metabolites with significant pharmaceutical applications due to their diverse biological activities (Atalar et al., 2023; Erenler, Atalar, et al., 2023; Erenler, Geçer, et al., 2022; Erenler, Karan, et al., 2023; Erenler, Yaman, et al., 2023; Yaman et al., 2022). Their importance in medicine and drug development stems from their antioxidant, anti-inflammatory, antimicrobial, anticancer, and neuroprotective properties (Bakchiche et al., 2024; Guemidi et al., 2024; Houari et al., 2024). Phenolics neutralize free radicals, reducing oxidative stress-related diseases such as cardiovascular disorders, diabetes, and neurodegenerative diseases (e.g., Alzheimer's, Parkinson's) (Erenler et al., 2014).

Flavonoids are widely found in plants and have the benzo-γ-pyrone structure. They are synthesized via the phenylpropanoid pathway and exhibit broad biological activity. Flavonoids scavenge free radicals and chelate metal ions, thus exhibiting antioxidant effects. Flavonoids can induce human protective enzyme systems. Numerous studies have suggested that flavonoids have protective effects against various infectious diseases (bacterial and viral) and degenerative diseases, including cardiovascular diseases, cancers, and other age-related conditions (Hadjra et al., 2023; Khodja et al., 2023; Ortiz et al., 2022).

Free radicals are reactive oxygen species produced by oxidative processes in the mammalian body (Gecer, 2023; Gecer et al., 2023). The human body has many defense mechanisms against oxidative stress. Under conditions such as poor lifestyle and exposure to environmental factors such as cigarette smoke and UV radiation, the body's antioxidant enzymes become insufficient. Excess free radicals damage the structure and function of the cell membrane, leading to conditions such as Alzheimer's, aging process, acute liver toxicity, cardiovascular disease, arteriosclerosis, nephritis, diabetes mellitus, rheumatism, inflammatory process and DNA damage that can lead to carcinogenesis (Erenler & Hosaflioglu, 2023). Many antioxidant-based drug formulations are used for the prevention and treatment of such diseases (Demirtas et al., 2013). In recent years, interest in natural antioxidants for use in the food, cosmetics, and pharmaceutical industries has increased due to the carcinogenic effects of synthetic antioxidants (Aissous et al., 2023; Zaoui et al., 2022). Antioxidant phytochemicals found in vegetables, fruits, and medicinal plants have received increasing attention due to their potential roles in disease prevention (Elmastas et al., 2004).

The *Trifolium* genus, which belongs to the Leguminosae family, comprises approximately 300 species. *Trifolium pratense* L. is an important forage plant widely grown in most temperate regions due to its high seedling vigor and fast growth characteristics. *Trifolium pratense* L. has potential applications in herbal dietary supplements, the treatment of menopausal symptoms, and the maintenance of bone and cardiovascular health. *Trifolium* species have been reported to display various biological activities. *T. alexandrinum* L. displayed antioxidative, hepatoprotective, and antibacterial properties, while *Trifolium angustifolium* L. revealed an antioxidant effect. *T. resupinatum* L. exhibited anti-inflammatory properties (Kolodziejczyk-Czepas, 2012). It has also recently attracted great attention due to its positive effects on the breast and endometrium (McKenna et al., 2018).

Here, a methanol extract of *Trifolium pratense* stem was prepared, and phenolic compounds were quantitatively analyzed. Moreover, the antioxidant activity of this extract was examined.

Material and methods

Plant material

Trifolium pratense was collected from the Iğdır University campus, and its botanical identification was carried out by Dr. Belkıs Muca Yiğit. A specimen was deposited in the Iğdır University Herbarium (No: INWM00000113).

Extraction and LC-ESI-MS/MS analysis

Trifolium pratense stem was powdered and extracted with methanol for 24 hours at room temperature. After removing the solvent, the crude extract was obtained. After the dilution from stock solution (1 mg/mL), the extract was subjected to LC-MS/MS analysis to quantify the phenolic compounds (Figure 1) (Başar et al., 2024).

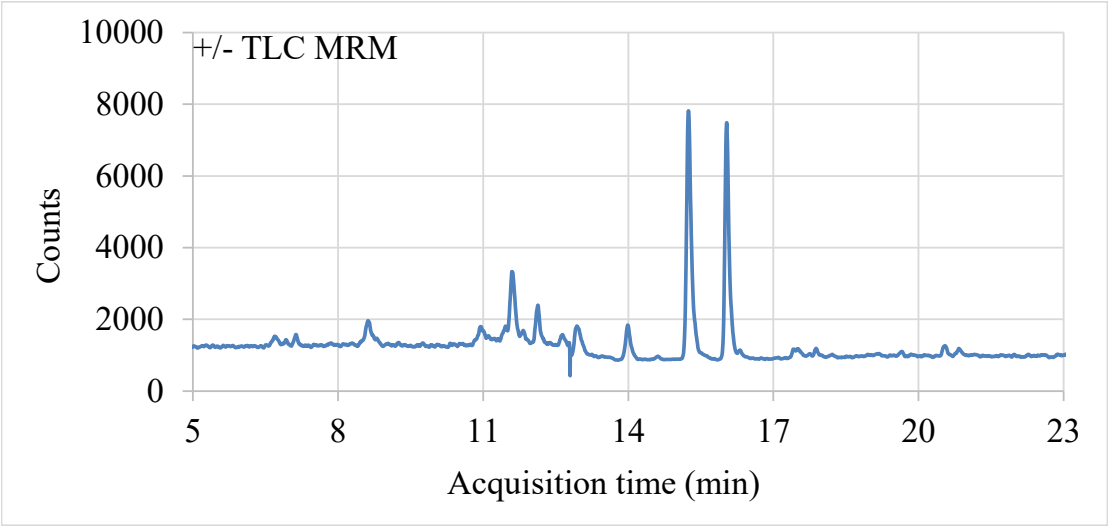

Figure 1. The MRM chromatogram *Trifolium pratense* stem

Antioxidant activity

Antioxidant activity of *Trifolium pratense* stem was carried out using the DPPH radical scavenging and ABTS cation scavenging assays. For the DPPH assay, samples at various concentrations were treated with a DPPH• solution in ethanol. Absorbance measurements were carried out at 517 nm, and the results were presented as IC_{50} values (Erenler et al., 2021). For the $ABTS^{\bullet+}$ radical cation scavenging assay, the different concentrations of samples were reacted with the $ABTS^{\bullet+}$ solution. The measurement was performed using a spectrophotometer at 734 nm. The results were calculated as IC_{50} (Genc et al., 2021).

Statistical analysis

GraphPad Prism (version 8.00) was used for the statistical analysis. A one-way ANOVA followed by Tukey multiple comparison tests was performed. The results were calculated as mean values ± standard deviation ($P < 0.05$).

Results and discussion

Quantitative analysis of phenolic compounds in plants is a significant area of research in natural product chemistry. A plant with a determined phenolic content will guide further scientific studies. Quantitative analysis of phenolic compounds in *Trifolium pratense* stem by LC-MS/MS was executed. Rutin (mg/g extract) (0.075), salicylic acid (0.044), trans-ferulic acid (0.004), gallic acid (0.003), and hesperidin (0.024) were determined as major compounds (Table 1).

Table 1. Quantitative analysis of natural compounds in *Trifolium pratense* stem by LC-MS/MS (mg/g extract)

No	Compound	RT	Quantity
1	Gallic acid	3.23	0.003
2	Chlorogenic acid	7.11	0.001
3	Hydroxybenzaldeyde	7.60	0.001
4	Caffeic Acid	7.77	0.001
5	Syringic acid	8.41	0.027
6	Vanillin	8.66	0.002
7	*o*-Coumaric acid	9.39	0.001
8	Salicylic acid	9.54	0.044
9	*t*-Ferulic acid	10.12	0.004
10	Sinapic acid	10.77	0.003
11	*p*-Coumaric acid	11.54	0.001
12	Coumarin	11.57	0.010
13	Hesperidin	11.84	0.024
14	Isoquercitrin	11.81	0.002
15	Rutin	12.39	0.075
16	Kaempferol-3-glucoside	13.29	0.003
17	Fisetin	13.44	0.002
18	Naringenin	15.07	0.004
19	Hesperetin	15.87	0.003
20	Kaempferol	16.12	0.010

nd: not detected, **RT**: retention time

Rutin is a significant natural compound found in many aromatic and medicinal plants, displaying a wide range of biological activities. The high concentration of rutin in *Trifolium pratense* stems provides the plant with high biological activity. Rutin (3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucoside) is a flavonol. Rutin has a large variety of biological activities such as sedative activity, anticonvulsant activity, anti-alzheimer activity, antidepressant effects, analgesic effect, antinociceptive effect, antiarthritic effects, antidiabetic effects, anti-hypercholesterolemic effects, anti-hypercholesterolemic effects, antiasthmatic activity, antiosteoporotic effect, antiosteopenic effect, anticataract effect, anticataract, anticancer effects, antibacterial activity, antifungal activities, antiviral activity, antifatigue activity, neuroprotective activity, retinoprotective activity, nephroprotective activity, wound healing activity (Ganeshpurkar et al., 2017).

The effects of salicylic acid (SA) on human health have been investigated for years. Salicylic acid, a phenolic compound, plays a vital role in plant defense against pathogens. It is found in fruits, vegetables, and spices in varying amounts. Salicylic acid is the primary metabolite and active

ingredient of acetylsalicylic acid, an anti-inflammatory drug used in clinical practice for over 100 years. In recent years, scientific studies have determined that acetylsalicylic acid is effective in preventing cardiovascular disease and colorectal carcinoma (Randjelović et al., 2015).

The antioxidant activity of *Trifolium pratense* stem was investigated using the DPPH and ABTS assays. The extract revealed the moderate DPPH activity (IC_{50}, 17.22 ± 0.67 µg/mL). The standard BHA and BHT activities were recorded as 5.47 ± 0.23 (IC_{50}, µg/mL) and 10.67 ± 0.20 (IC_{50}, µg/mL), respectively. The same trend was observed for the ABTS assay. The extract activity was determined as 9.03 ± 0.11 µg/mL (IC_{50}). BHT activity was detected as 9.51 ± 0.25 µg/mL (IC_{50}) (Figure 2).

Previous studies reported that the plants had antioxidant activity due to their secondary metabolite contents. *Rubia tinctorum* L. essential oils were reported to reveal considerable antioxidant activity (Houari et al., 2024). Plants have been used for synthesis of nanoparticles (Dag, 2022; Erenler & Dag, 2022; Gecer, 2021). Bioactive compounds in plants act as reducing, stabilizing and capping agents (Erenler & Gecer, 2022a, 2022b; Gecer & Erenler, 2022a). Due to the properties of nanoparticles and bioactive compounds capped the silver ions, nanoparticles were observed to display the considerable antioxidant activity (Gecer & Erenler, 2022b; Gecer, Erenler, et al., 2022; Sahin Yaglioglu et al., 2022).

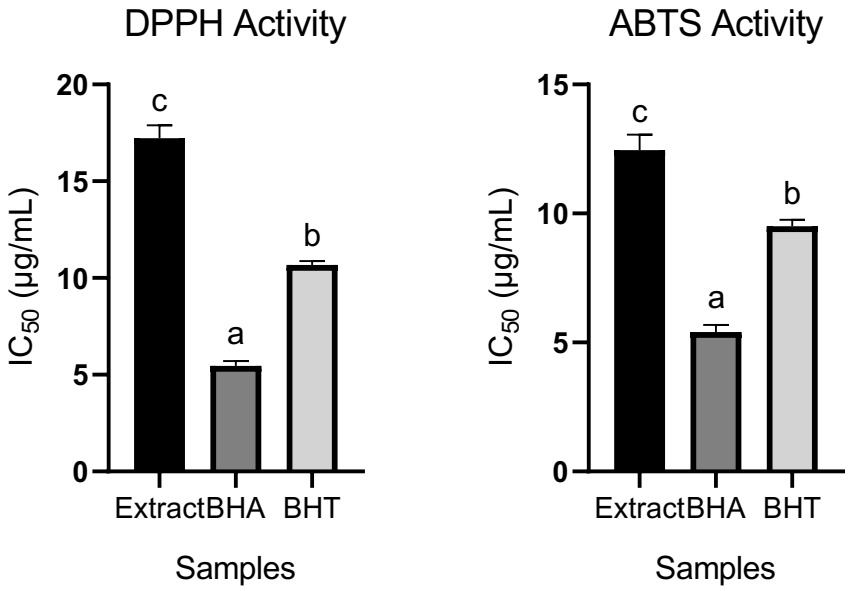

Figure 2. Antioxidant activity of *Trifolium pratense* stem. Means (three replicates) followed by different letters (a, b, and c) express a statistical difference ($P < 0.05$).

Conclusions

The phytochemistry of *Trifolium pratense* stem was evaluated. Quantitative analysis of phenolics was executed. The pharmaceutically significant compounds were determined as major products. Hence, this study will guide the synthesis chemist for further studies. The high concentrated compounds in *Trifolium pratense* stem such as rutin, salicylic acid, *t*-ferulic acid, gallic acid, and hesperidin can be isolated by chromatographic methods and their structures can be identified by spectroscopic techniques. The usability of *Trifolium pratense* stem extract in food supplement can be investigated.

Author contributions

R.E. and E.N.G. designed the study. R.E. interpreted the results and wrote the manuscript. I.Y. and S.M.C. carried out the experiment. I.H. collected and deposited the plant material.

Declaration of interests

The authors declare that there is no conflict of interest.

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Kuru ve taze *Arum maculatum* bitkisinden elde edilen dekoksiyon ve etanol ekstrelerinin fenolik içerik analizi ve antioksidan aktivitesi

Phenolic content analysis and antioxidant activity of decoction and ethanolic extracts obtained from dried and fresh *Arum maculatum*

Ezgi Keskin, Duygu Mısırlı, Mahfuz Elmastaş*

Sağlık Bilimleri Üniversitesi, Hamidiye Eczacılık Fakültesi, İstanbul, Türkiye

ÖZET

Arum maculatum L., Araceae familyasına ait, Avrupa, Batı-Asya ve Kuzey Afrika'da doğal yayılış gösteren, toksik özelliklerine rağmen geleneksel tıpta yaygın olarak kullanılan çok yıllık otsu bir bitkidir. Türkiye'de halk arasında hemoroid, karaciğer rahatsızlıkları ve sindirim sistemi sorunlarının tedavisinde tercih edilmekte; yaprakları sebze olarak tüketilmektedir. Yapılan literatür araştırmamızda, *A. maculatum*'un özellikle yenilebilir formlarındaki fenolik içerik ve antioksidan potansiyeline yönelik kantitatif çalışmalar sınırlıdır. Bu nedenle mevcut çalışmada, *A. maculatum*'un Samsun yöresinde geleneksel olarak gıda şeklinde kullanılan taze ve kuru herbadan elde edilen etanol:su ve dekoksiyon ekstrelerinin *in vitro* antioksidan aktiviteleri ile fenolik bileşik profilleri kantitatif olarak incelenmiştir. Antioksidan aktivite DPPH• ve CUPRAC yöntemleriyle değerlendirilmiş; en yüksek DPPH• radikal giderme aktivite ve CUPRAC indirgeme gücü, kuru bitki etanol:su ekstresinde (E1) sırasıyla %34,5 ve 0,27 mmol TE/g olarak saptanmıştır. HPLC analizleriyle gallik asit, klorojenik asit ve kuersetin tüm ekstrelerde tespit edilmiş; apigenin-7-O-glukozit yalnızca E1'de bulunmuştur. Bu bulgular, fenolik bileşik miktarı ve çeşitliliğinin, ekstraksiyon yöntemine ve bitki materyalinin işlenme durumuna bağlı olarak değiştiğini göstermektedir. Elde edilen veriler, *A. maculatum*'un fenolik içeriği zengin doğal bir antioksidan kaynağı olabileceğini ve geleneksel kullanımlarını bilimsel olarak desteklediğini ortaya koymaktadır.

Anahtar kelimeler: *Arum maculatum*, dekoksiyon, etanol:su ekstre, antioksidan aktivite, HPLC, fenolik bileşik

ABSTRACT

Arum maculatum L., a member of the Araceae family, is a perennial herbaceous plant naturally distributed in Europe, Western Asia, and North Africa. Despite its toxic properties, it has been widely used in traditional medicine for haemorrhoids, liver disorders, and digestive system ailments. In Türkiye, its leaves are also consumed as a vegetable. According to our literature review, quantitative studies focusing on the phenolic content and antioxidant potential of *Arum maculatum*, particularly in its edible forms, are limited. Therefore, the present study aims to investigate the *in vitro* antioxidant activity and quantitatively phenolic compound profile of decoction and ethanolic extracts obtained from the fresh and dried aerial parts of *A. maculatum*, traditionally used in the Samsun region. Antioxidant activity was assessed using DPPH• and CUPRAC assays. The highest DPPH radical scavenging activity and CUPRAC reducing power were observed in the ethanolic extract of the dried plant (E1), with values of 34.5% and 0.27 mmol TE/g extract, respectively. HPLC analyses revealed that gallic acid, chlorogenic acid, and quercetin were present in all extracts, while apigenin-7-O-glucoside was detected exclusively in E1. The findings indicate that both the quantity and diversity of phenolic compounds vary depending on the extraction method and plant material processing. These results suggest that *A. maculatum* may serve as a rich natural source of antioxidants and provide scientific support for its traditional medicinal uses.

Keywords: *Arum maculatum*, decoction, ethanolic extract, antioxidant activity, HPLC, phenolic compound

***İletişim:**
mahfuz.elmastas@sbu.edu.tr

ORCID iD:
0000-0002-1502-1141

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Giriş ve amaç

Arum L. cinsi, Araceae familyasına ait olup, Avrupa, Batı ve Orta Asya ile Kuzey Afrika'da doğal olarak yetişen 29 türü kapsamaktadır. Bu cinse ait türler, Türkiye'de yaygın olarak "yılan yastığı", "yavruğan" veya "domuz pastırması" gibi adlarla bilinmekte ve halk arasında hem tıbbi hem de besin amaçlı olarak çeşitli şekillerde kullanılmaktadır. Bu cinsin en bilinen türlerinden biri olan *Arum maculatum* L. çok yıllık, yaprak döken ve ormanlık alanlarda yetişen bu bitki; Avrupa, Doğu Ukrayna ve Anadolu'da yayılış göstermektedir (Sowter, 1949). Bitkinin yumruları yatay eksende, düzensiz silindirik formdadır ve sürgünler bu eksenin ucundan çıkar. *A. maculatum* yapraklar ok şeklinde ve uzun saplı olup yeşil renklidir. Ham haliyle bitki, toksik ve alerjenik özellikleri nedeniyle yenilebilir değildir. Cilt, ağız, dil ve boğazda tahrişe neden olabileceği; boğazda şişme, solunum güçlüğü, yanma hissi ve karın ağrısı gibi semptomlara yol açabileceği bildirilmiştir (Tamilselvan vd., 2014). Bu olumsuz etkilerine rağmen, bitki birçok hastalığın tedavisinde terapötik açıdan önemli bir yere sahiptir ve geleneksel olarak böbrek rahatsızlıkları, karaciğer hasarları, hemoroid tedavisi ile analjezik (ağrı kesici) amaçlarla kullanıldığı bildirilmiştir (Abbasi vd, 2014; Kochmarov vd., 2015). Sonbaharda olgunlaşan ve turuncu-kırmızı renkte olan meyveleri, cilt ve mukoz membran üzerinde ağrı ve tahrişe neden olan oksalat kristalleri içerir (Erbil vd., 2018).

Arum türlerinin köklerinin arkaik çağlarda besin olarak tüketildiği bilinmektedir. Orta Çağ'da bitkinin geleneksel kullanımları arasında balgam söktürücü, solucan düşürücü ve terletici etkileri nedeniyle tıbbi halk arasında kullanılmıştır (Çolak, Savaroğlu ve İlhan, 2009). Materia Medica kayıtlarına göre bitki, yılan sokmalarına karşı bir tedavi yöntemi olarak kabul edilmiştir. *Arum maculatum*, Francesc Bolòs'a ait herbaryum kayıtlarında da tıbbi bitki olarak yer almaktadır. Bu kayıtlarda bitkinin balgam söktürücü, astım önleyici ve cinsel yolla bulaşan hastalıklara karşı kullanımı belgelenmiştir. Bitkinin yakıcı etkisi ise toksik özelliği olarak kaydedilmiştir (Gras vd., 2017). 17. yüzyılda ise sıtma, veba ve mide ile solunum sisteminde balgamın giderilmesi amacıyla kullanılmıştır (Kochmarov vd., 2015). Toz haline getirilmiş *Arum maculatum* köklerinin düşük dozlarda terletici (diyaforetik) etki gösterdiği, ancak yüksek dozlarda toksik özellik taşıdığı bildirilmiştir. Ayrıca, meyvelerinin özellikle çocuklar için ölümcül olabileceği belirtilmiştir (Atalay ve Yıldız, 2020).

Modern etnofarmakolojik çalışmalar, *A. maculatum*'un Balkanlar, Türkiye ve çevresinde hâlen halk hekimliğinde kullanıldığını ortaya koymaktadır. Bu bağlamda bitkinin en sık kullanıldığı alanlardan biri hemoroid tedavisidir. Konvansiyonel tıpta cerrahi müdahaleler ve flavonoid içeren ilaçlar (örneğin diosmin) tedaviye dahil edilmekle birlikte, halk arasında bitkisel çözümler tercih edilmeye devam etmektedir. Literatürde, bitkinin çeşitli kısımlarının halk arasında tedavi amaçlı kullanımları arasında antihipertansif, antiromatizmal, antihemoroidal, analjezik, antidiyabetik etkiler ile bunların yanı sıra yanıklar ve yaralara, boğaz ağrısı ve soğuk algınlığına karşı kullanımı da yer almaktadır (Kozuharova vd., 2020). Kanser tedavisinde kullanılan bitkiler üzerine yapılan bir etnobotanik çalışmada, *A. maculatum* yaprakları kullanıldığı ve bundan hazırlanan dekoksiyonun geleneksel olarak tüketildiği belirlenmiştir (Abu-Darwish ve Efferth, 2018). Ürdün'de halk hekimliğinde bitkinin hem gıda hem de doğum kontrolü amacıyla kullanıldığı rapor edilmiştir. Fas'ta ise toz haline getirilmiş köklerinin mide rahatsızlıklarına karşı kullanıldığı rapor edilmiştir (Nabeel, Abderrahman ve Papini, 2008; El-Hilaly, Hmammouchi ve Lyoussi, 2003). Türkiye'de, *A. maculatum* yapraklarının antiinflamatuar ve sindirim sistemi düzenleyici olarak kullanıldığı; ayrıca gut, karaciğer, solunum sistemi rahatsızlıkları, eklem ağrıları, hemoroid ve romatizmal hastalıklara karşı da kullanıldığı belirlenmiştir (Tetik, Civelek ve Cakilcioglu, 2013). Bitkinin yaprakları sebze olarak tüketilmekte, bu yapraklar buğday veya pirinç ile doldurularak veya kavrularak yemek şeklinde pişirilmektedir (Dogan vd., 2004).

Arum maculatum, geleneksel halk hekimliğinde yaygın olarak kullanılan ve çok sayıda etnobotanik çalışmaya konu olmuş bir bitkidir. Bu çalışmada, *A. maculatum*'un Samsun'da halk arasında gıda olarak kullanılan şekline uygun dekoksiyon ve etanol:su ekstrelerinin *in vitro* antioksidan aktivitesinin ve fenolik bileşik profilinin kantitatif olarak araştırılması amaçlanmıştır.

Materyal ve metot

Bitki materyali

Arum maculatum bitkisi Ezgi Keskin tarafından Samsun'dan temin edildi. Bitki ile ilgili tür teşhisi Hatay Mustafa Kemal Üniversitesi Fen Edebiyat Fakültesi Biyoloji Bölümü öğretim üyelerinden Prof. Dr. Ahmet İlçim tarafından yapılmıştır.

Ekstrelerin hazırlanması

Arum maculatum taze ve kurutulmuş bitki kısımları ekstreleri aşağıda verildiği gibi hazırlandı. Kuru bitki formu laboratuvar tipi öğütücü ile toz edildikten sonra ekstre hazırlandı. Taze bitki, blender ile parçalandıktan sonra ekstraksiyon için kullanıldı.

Etanol ekstresi için hem taze hem de kurutulmuş bitki kısımlarından ayrı ayrı 10 g alınarak cam balona alınarak üzerine 250 mL etanol:su (80:20) ilave edildi. Ağzı gevşek bir

şekilde kapatılarak, oda sıcaklığında iki saat orbital çalkalayıcı ile karıştırıldıktan sonra çözücü kısmı başka bir kaba alınarak posa üzerine tekrar aynı miktarda etanol:su (80:20) ilave edilerek işlem tekrarlandı. Bu işleme renk berraklaşıncaya kadar devam edildi. Daha sonra etanol, rotary evaporatör ile düşük basınç altında uzaklaştırıldı. En son kalan sulu kısım, liyofilizatör ile uzaklaştırılarak etanol:su ekstre elde edildi. Kuru bitki etanol:su ekstre E1 olarak kodlandı. Taze bitki etanol:su ekstre E2 olarak kodlandı.

Dekoksiyon için taze bitki kullanıldı. Taze bitki parçalandıktan sonra 10 g alınarak cam balona alınarak üzerine 250 mL saf su ilave ederek yarım saat açık hava atmosferinde 30 dakika kaynatıldı. Oda sıcaklığına geldikten sonra filtre kağıdından geçirilerek süzüldü. Daha sonra bu süzüntü dondurarak kurutma yöntemi ile liyofilize edildi. Taze bitki dekoksiyon ekstre E3 olarak kodlandı.

Elde edilen bu ekstreler hem fenolik bileşik profil analizi hem de antioksidan aktivite analizleri için kullanıldı.

Fenolik bileşik profilinin kantitatif analizi

Fenolik bileşiklerin kantitatif ve kalitatif analizleri, Yüksek Performanslı Sıvı Kromatografisi (HPLC) yöntemi kullanılarak gerçekleştirilmiştir. Analizler, Sağlık Bilimleri Üniversitesi Fitoterapi Araştırma Laboratuvarı'nda, Shimadzu Nexera-i LC-2040C 3D Plus marka HPLC cihazı ile yürütülmüştür. Dedektör olarak Photo Diode Array (PDA) dedektörü tercih edilmiş; kromatografik ayrım, 3 µm partikül büyüklüğüne sahip, 4,6 mm x 150 mm boyutlarında, C6 fenilheksil ters faz kolonda sağlanmıştır.

Mobil faz sistemi iki çözücüden oluşturulmuştur: Mobil Faz A olarak %0.1 formik asit içeren saf su, Mobil Faz B olarak ise asetonitril kullanılmıştır. Elüsyon, gradyan programı ile gerçekleştirilmiştir. Programın başlangıcında (0.01. dakikada), mobil faz B oranı %5, mobil faz A oranı %95 olarak ayarlanmıştır. Yedinci dakikada bu oranlar sırasıyla %9,5 (B) ve %90,5 (A); yirminci dakikada %17 (B) ve %83 (A); otuz beşinci dakikada ise %40 (B) ve %60 (A) olacak şekilde değiştirilmiştir. Analiz süresi toplam 40,01 dakika olup, bu sürenin sonunda mobil faz tamamen %100 A fazına dönüştürülerek sistem sonlandırılmıştır. Kolon sıcaklığı 30 °C'ye sabitlenmiş, mobil faz akış hızı ise 1 mL/dakika olarak belirlenmiştir.

Her bir ekstrakt için 1000 µg/mL konsantrasyonunda stok çözeltiler hazırlanmıştır. Ticari olarak temin edilen standart fenolik bileşiklerden farklı konsantrasyonlarda çözeltiler hazırlanarak, her bir bileşiğin alıkonma (retention) zamanları belirlenmiştir (Ataseven vd., 2021). Çalışmada analiz edilen 15 fenolik bileşik şunlardır: gallik asit, epikateşin, sinnamik asit, 4-hidroksibenzoik asit, rutin, kuersetin, klorojenik asit, kafeik asit, ferulik asit, kikorik asit, *p*-kumarik asit, vanilik asit, apigenin-7-O-glukozit, salisilik asit ve naringenin. Her bir bileşik, PDA dedektörü aracılığıyla, maksimum absorbans dalga boylarında incelenmiştir. Standart çözeltiler +4 °C'de muhafaza edilmiştir.

Ekstrelerde bu 15 fenolik bileşiğin taraması yapılmış, tespit edilen bileşikler için miktar tayini gerçekleştirilmiştir. Sonuçlar, mg/g ekstre cinsinden kantitatif olarak raporlanmıştır.

Antioksidan aktivite analizleri

Serbest radikal giderme aktivitesinin belirlenmesi

Antioksidan kapasitenin belirlenmesinde 2,2-Difenil-1-pikrilhidrazil (DPPH•) radikali kullanılarak serbest radikal giderme aktivitesi ölçülmüştür. Bu amaçla, 1 mM DPPH• çözeltisi hazırlanmıştır. Her bir ekstreden 1 mg/mL olacak şekilde stok çözelti hazırlanmıştır. Bu stok çözeltiden seri dilüsyon yöntemiyle 250, 200, 100, 50 ve 25 µg ekstre/mL konsantrasyonlarında olacak şekilde hazırlanarak analizler yapılmıştır.

Mikroplaka tabanlı analizde, kör (blank) bir kuyucuğa 200 µL etanol, kontrol için ise bir başka kuyucuğa 200 µL DPPH• (1 mM) çözeltisi eklenmiştir. Diğer kuyucuklara 10 µL örnek ekstre çözeltileri ilave edilmiş, ardından her birine 190 µL DPPH• çözeltisi eklenmiştir. Tüm plakalar 30 dakika boyunca karanlık ortamda inkübe edilmiştir. İnkübasyon süresi sonunda absorbans değerleri, 517 nm dalga boyunda, köre karşı spektrofotometrik olarak ölçülmüştür (Brand-Williams vd., 1995).

Örneklerin serbest radikal giderme kapasiteleri, aşağıda verilen formül kullanılarak yüzde inhibisyon (%) cinsinden hesaplanmıştır.

DPPH• radikali giderme aktivitesi:

$((A_{kontrol}-A_{numune})/A_{kontrol}) \times 100$

Burada,

$A_{kontrol}$ sadece DPPH• içeren pozitif kontrolün absorbansını,

A_{numune} örnek içeren kuyucukların absorbansını temsil etmektedir.

Bakır (II) iyonu indirgeyici antioksidan kapasite (CUPRAC)

Bitki ekstrelerinin indirgeme gücünü belirlemek amacıyla CUPRAC (Cupric Reducing Antioxidant Capacity) yöntemi kullanılmıştır (Özyürek vd., 2011). CUPRAC analizinde kullanılan reaktiflerin hazırlanması aşağıdaki şekilde gerçekleştirilmiştir. 33,63 mg $CuCl_2$ tartılarak 25 mL saf su içerisinde çözülmüş ve Cu(II) çözeltisi hazırlanmıştır. Aynı şekilde, 39 mg neokuproin tartılarak 25 mL saf su ile balon

jojede tamamlanarak neokuproin çözeltisi elde edilmiştir. Asetat tampon çözeltisi hazırlamak amacıyla 1,93 g amonyum asetat 25 mL saf su içerisinde çözülmüş ve pH değeri 7,0 olacak şekilde ayarlanmıştır.

Standart çözeltiler, daha önceden hazırlanmış 8 mM Trolox stok çözeltisinden seri dilüsyon yöntemiyle 1; 0,5; 0,25; 0,10; 0,05 mM konsantrasyonlarında hazırlanmıştır. Ekstre çözeltileri ise 400 µg/mL konsantrasyonunda hazırlanarak analizler gerçekleştirilmiştir. Mikroplaka üzerindeki ölçümler için negatif kontrol kuyucuğuna sırasıyla 50 µL $CuCl_2$ çözeltisi, 50 µL neokuproin çözeltisi, 50 µL tampon çözelti ve 100 µL saf su eklenmiştir. Diğer tüm kuyucuklara ise aynı sıralama ile 50 µL $CuCl_2$, 50 µL neokuproin ve 50 µL tampon çözelti ilave edilmiştir. Bu karışımlar 37 °C sıcaklıkta 15 dakika boyunca inkübe edilmiştir. İnkübasyonun ardından her bir kuyucuğa 100 µL standart veya örnek çözeltisi eklenmiş ve ilave olarak 5 dakika daha inkübe edilmiştir. Reaksiyon sonunda absorbans değerleri 450 nm dalga boyunda, negatif kontrole karşı olacak şekilde spektrofotometrik olarak ölçülmüştür.

Trolox'un farklı konsantrasyonlarına karşı elde edilen absorbans değerleri ile kalibrasyon eğrisi oluşturulmuş ve bu eğrinin denkleminden yararlanılarak bitki ekstrelerinin indirgeme kapasiteleri hesaplanmıştır. Sonuçlar, gram ekstre başına milimol Trolox eşdeğeri (mmol TE/g ekstre) cinsinden ifade edilmiştir.

Bulgular

Fenolik bileşik analiz bulguları

Arum maculatum ekstrelerinin HPLC-PDA ile analizini gerçekleştirebilmek amacıyla öncelikle hareketli faz sistemi, kolon, kolon sıcaklığı, dedektör dalga boyları ve akış hızı gibi kromatografik parametreler belirlendi. Kromatografik analizler optimize edildi. Kantitatif olarak analizi yapılan fenolik bileşiklerin metot validasyonu yapılarak Tablo 1 verilmiştir.

Tablo 1. Tespit edilen fenolik bileşiklerin kantitatif analiz şartları

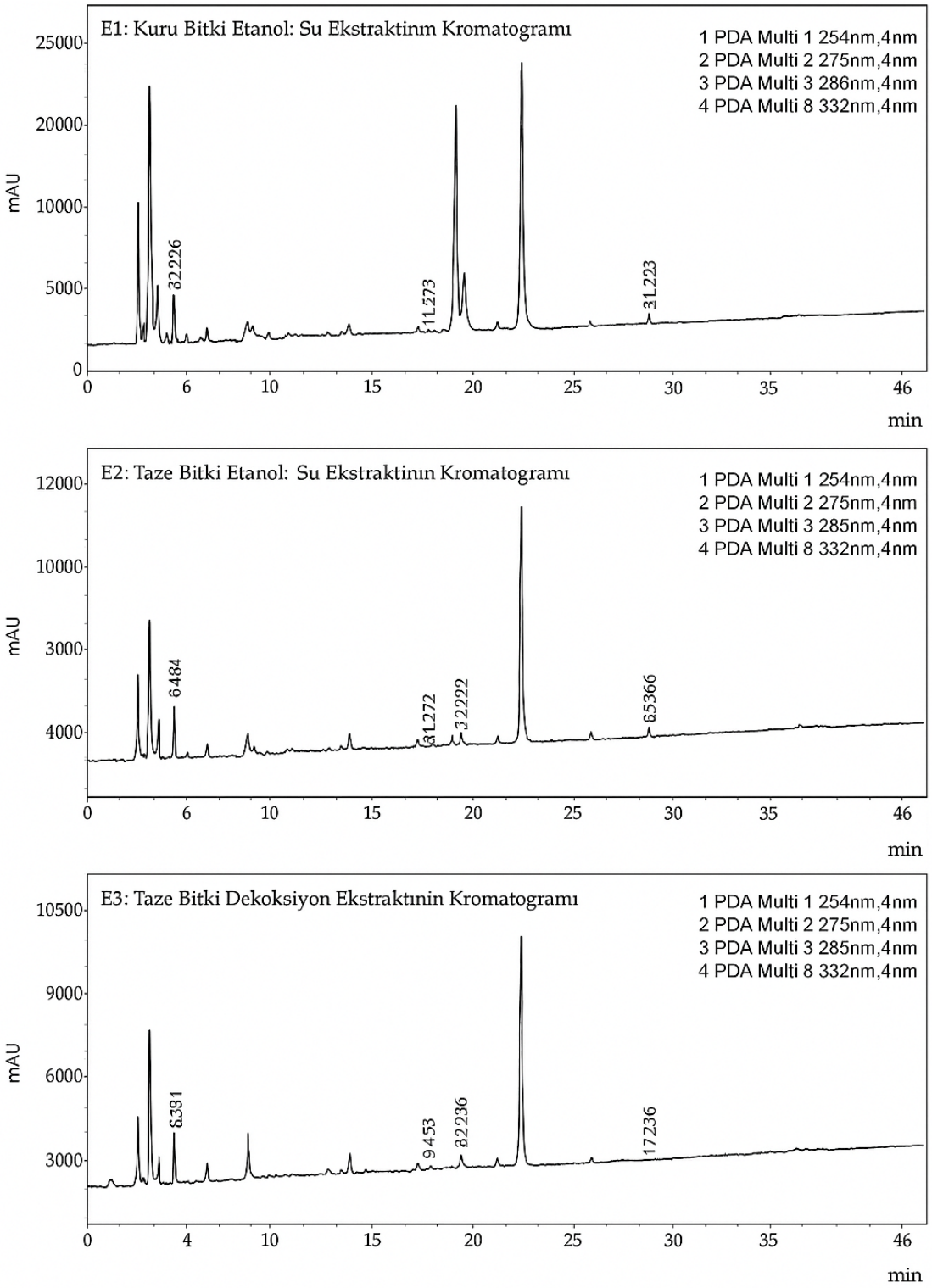
Fenolik Bileşik Adı	Alıkonma Zamanı (dk)	Birim	Maksimum Dalga Boyu (nm)	Kalibrasyon Denklemi	R^2	Tespit Limiti (LOD mg/L)	Miktar Tayini Limiti (QOD, mg/L)
Gallik asit	4,352	mg/L	271nm	y=29799,9x+6494,60	0,9995	0,7440	2,2547
Klorojenik asit	12,073	mg/L	325nm	y=28066,0x+25870,2	0,9990	1,3687	4,1476
Ferulik asit	20,971	mg/L	322nm	y=46665,0x-14606,2	0,9928	1,3865	4,2016
Apigenin-7-O-glukozit	27,574	mg/L	336nm	y=39321,9x+1685,18	0,9993	0,7295	2,2107
Kuersetin	32,008	mg/L	254nm	y=26403,4x+1558,71	0,9997	1,2724	3,8560

Hazırlanan ekstrelerden HPLC cihazına verilmek üzere örnekler hazırlandı. E1, E2 ve E3 kodlu ekstrelerin her biri 1 mg/mL olacak şekilde stok çözeltiler başlangıç HPLC hareketli fazı ile hazırlandı. Hazırlanan örnekler vortekslendi ve her örnekten 2 mL alınarak viallere konuldu. 30°C kolon sıcaklığında 40 dk boyunca analiz edildi. Elde edilen sonuçlar Tablo 2'de verilmiştir. Her bir ekstrenin HPLC kromatogramı Şekil 1'de verilmiştir.

Tablo 2. Ekstrelerden tespit edilen fenolik bileşikler

Fenolik Bileşik İsmi	Alıkonma Zamanı	Birim	E1	E2	E3
Gallik Asit	4,352	mg/g Ekstre	1,459	0,563	1,092
Klorojenik Asit	12,,073	mg/g Ekstre	0,977	0,88	0,79
Ferulik Asit	20,971	mg/g Ekstre		0,653	0,186
Apigenin-7-O-glukozit	27,574	mg/g Ekstre	0,052		
Kuersetin	32,008	mg/g Ekstre	0,541	0,622	0,128

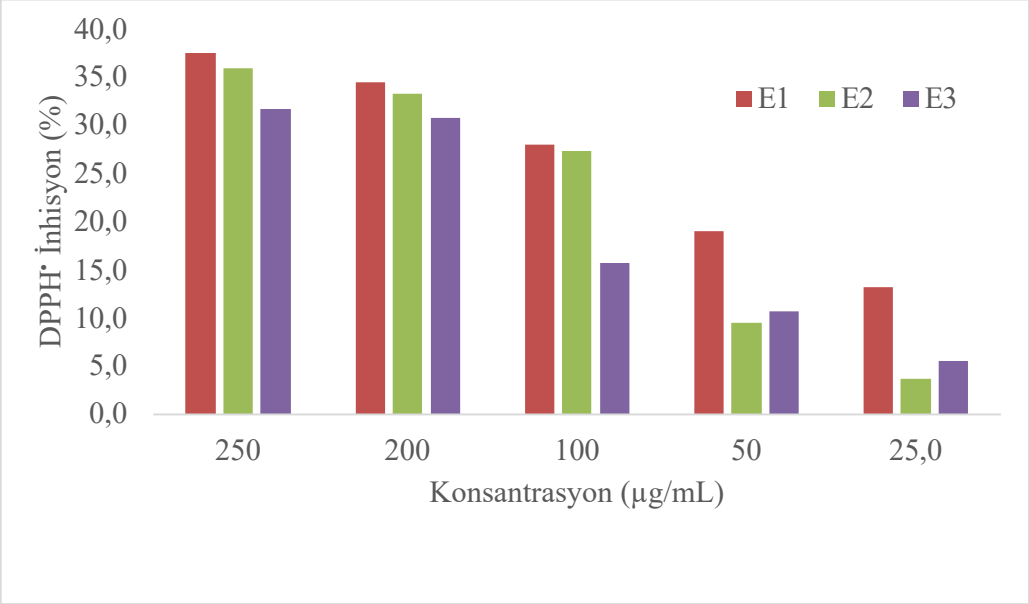
Her bir ekstrede standart olarak 15 farklı fenolik bileşiklerin taraması yapıldı. Bu bileşikler gallik asit, epikateşin, sinnamik asit, 4-hidroksibenzoik asit, rutin, kuersetin, klorojenik asit, kafeik asit, ferulik asit, kikorik asit, *p*-kumarik asit, vanilik asit, apigenit-7-O-glukozit, salisilik asit ve naringenindir. Tüm ekstrelerde gallik asit, klorojenik asit ve kuersetin bulunurken ferulik asit E2 ve E3 ekstrelerinde miktarı bulunmuştur. Apigenin-7-O-glukozit ise sadece kuru bitki etanol ekstresinde (E1) tespit edildi. Ekstrelerde bulunan fenolik bileşiklerin miktarları Tablo 2'de verilmiştir.



Şekil 1. Ekstrelerin HPLC analizlerinde elde edilen kromatogramlar

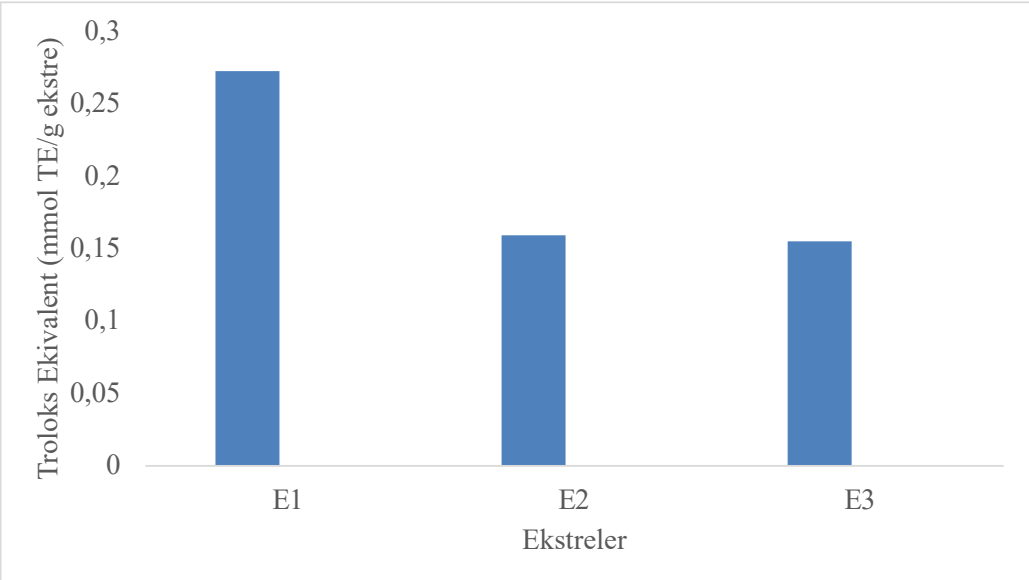
Arum maculatum ekstrelerinin antioksidan aktivite bulguları

Antioksidan aktivite analizleri için DPPH• radikal giderme aktivite ve CUPRAC yöntemleri kullanıldı. DPPH• analizinde yüzde (%) inhibisyon değerleri hesaplandı. Elde edilen bulgulara göre 200 µg/mL konsantrasyonlardaki DPPH• radikal giderme aktivite değerleri yüzde olarak; kuru bitki etanol:su ekstre (E1), taze bitki etanol:su ekstre (E2) ve taze bitki dekoksiyon ekstre (E3) sırasıyla 34,5; 33,3; 30,8 µg/mL olarak bulunmuştur. Bu durumda E1 ekstresi en yüksek aktiviteye sahip iken en düşük aktivite E3 ekstresinde olduğu gözlemlenmiştir (Şekil 2).



Şekil 2. Ekstrelerin DPPH analiz bulguları

CUPRAC deneyinde indirgeme gücü mmol TE/g Ekstre cinsinden hesaplanmıştır. Elde edilen bulgulara göre 400 µg/mL konsantrasyonlardaki CUPRAC aktivite değerleri; kuru bitki etanol:su ekstre (E1), taze bitki etanol:su ekstre (E2) ve taze bitki dekoksiyon ekstre (E3) sırasıyla 0,27; 0,16 ve 0,15 olarak tespit edilmiştir (Şekil 3).



Şekil 3. Ekstrelerin CUPRAC analiz bulguları

Sonuç ve tartışma

Bu çalışmada, *Arum maculatum* bitkisinin taze ve kuru herbasından elde edilen etanol:su ve dekoksiyon ekstrelerinin antioksidan aktiviteleri ve fenolik bileşik içerikleri karşılaştırmalı olarak değerlendirilmiştir. Antioksidan aktivite belirteci olarak DPPH• radikal giderme ve CUPRAC yöntemleri tercih edilmiştir. DPPH• analizine göre, kuru bitki etanol:su ekstresi (E1), %34,5 inhibisyon değeri ile en yüksek antioksidan aktiviteye sahipken, taze bitki dekoksiyon ekstresi (E3) %30,8 ile en düşük aktiviteyi göstermiştir. CUPRAC analizinde ise yine E1 ekstresi 0,27 mmol TE/g değer ile en yüksek indirgeme gücüne sahip olmuş, E2 ve E3 ekstreleri ise sırasıyla 0,16 ve 0,15 mmol TE/g değerleriyle daha düşük seviyelerde kalmıştır.

Bu sonuçlar, bitkinin kurutulmuş formunun etanol:su ekstraksiyon ile elde edilen ekstrenin, antioksidan bileşikleri daha yoğun içerdiğini göstermektedir. Literatürde, bitkisel materyalin kurutulmasının bazı fenolik bileşiklerin serbest hale geçmesini kolaylaştırarak antioksidan potansiyeli artırabileceği belirtilmektedir (Molyneux, 2004; Singleton vd., 1999). Aynı zamanda, sıcaklıkla uygulanan dekoksiyon işlemlerinin bazı fenolik bileşikleri parçalayabileceği ve böylece aktivitenin azalabileceği bilinmektedir (Dai ve Mumper, 2010).

Fenolik bileşik analizleri, ekstraktların antioksidan aktiviteleri ile fenolik içerikleri arasında anlamlı bir korelasyon olabileceğini ortaya koymaktadır. Bu durum literatürde sıklıkla bildirilen bir bulgudur; birçok çalışma, fenolik bileşiklerin özellikle hidroksil gruplarının serbest radikalleri stabilize etme yetenekleri sayesinde güçlü antioksidan özellikler sergilediğini belirtmiştir (Rice-Evans vd., 1996; Balasundram vd., 2006).

Bu çalışmada gallik asit, klorojenik asit ve kuersetin gibi iyi bilinen antioksidan bileşiklerin tüm ekstraktlarda tespit edilmiş olması, bu bileşiklerin bitkinin antioksidan kapasitesine önemli ölçüde katkı sağladığını göstermektedir. Elde edilen verilere göre gallik asit miktarı kuru bitki etanol:su ekstresinde (E1) 1,459 mg/g iken, taze bitki etanol:su (E2) ve dekoksiyon (E3) ekstrelerinde sırasıyla 0,563 ve 1,092 mg/g olarak belirlenmiştir. Bu sonuç, gallik asitin ekstraksiyon veriminin kurutulmuş bitki materyalinde daha yüksek olduğunu desteklemektedir. Benzer şekilde, klorojenik asit miktarları da E1 ekstraktında (0,977 mg/g) daha yüksek bulunmuştur. Literatürde, kurutma işleminin hücre duvarlarının geçirgenliğini artırarak fenolik bileşiklerin ekstraksiyonunu kolaylaştırdığı bildirilmiştir (Dai ve Mumper, 2010; Wojdyło vd., 2007).

Dikkat çekici bir diğer bulgu ise yalnızca E1 ekstresinde tespit edilen apigenin-7-O-glukozit bileşiğidir. Bu durum, kuru bitkiden etanol ile yapılan ekstraksiyonun yalnızca miktar açısından değil, fenolik çeşitlilik açısından da daha zengin olduğunu ortaya koymaktadır. Ayrıca kuersetin miktarının taze bitki etanol:su ekstresinde (0,622 mg/g), kuru bitki ekstraktına (0,541 mg/g) göre daha yüksek olması; bazı fenoliklerin taze bitki formunda daha stabil kaldığını veya sıcaklık etkisiyle parçalanmadan ekstrakte edilebildiğini düşündürmektedir (Manach vd., 2004).

Genel olarak, bu bulgular bitkisel ekstraktların antioksidan kapasitelerinin yalnızca fenolik toplam miktarına değil, aynı zamanda bileşiklerin spesifik türlerine ve ekstraksiyon koşullarına bağlı olarak değişkenlik gösterebildiğini ortaya koymaktadır.

Elde edilen bulgular genel olarak, *Arum maculatum* bitkisinin etanol:su ekstraksiyonla elde edilen kuru bitki ekstresinin, hem toplam fenolik içerik hem de antioksidan aktivite açısından daha avantajlı olduğunu göstermektedir. Bu bağlamda, E1 ekstresi potansiyel doğal antioksidan kaynağı olarak değerlendirilmelidir. Bununla birlikte, farklı ekstraksiyon yöntemleriyle ve farklı bitki kısımlarıyla yapılacak ileri çalışmalar, bileşiklerin biyoyararlanımı ve sinerjik etkileri hakkında daha kapsamlı bilgiler sunabilir.

Yazar katkıları

Ezgi Keskin, bitkinin temin edilmesi, ekstrelerin hazırlanması ve antioksidan aktivite analizlerinin yapılmasında görev aldı. Duygu Mısırlı, HPLC analizlerin yapılması ve değerlendirilmesinde görev aldı. Mahfuz Elmastaş, antioksidan aktivite analiz yorumlanması ve makale yazımında görev aldı.

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Chemical components, antidiabetic and anticancer effects of *Origanum* species

Origanum türlerinin kimyasal bileşenleri, antidiyabetik ve antikanser etkileri

Merve Nur Bay, Ali Şen*, Leyla Bitiş

Department of Pharmacognosy, Faculty of Pharmacy, Marmara University, İstanbul, Türkiye

ABSTRACT

Cancer and diabetes are two of the most common chronic diseases in people worldwide. Developing countries in particular, still rely on herbs as supportive or complementary therapies in the treatment of these diseases. The aim of this study is to review the phytochemical content and studies on the antidiabetic and anticancer effects of *Origanum* genus, which is safely used as spice and tea and is one of the important genera for Türkiye, and to reveal the importance of this species in terms of health. For this purpose, important databases such as ScienceDirect, Springer, Web of Science, Wiley Online Library, Taylor & Francis, Google Scholar were searched. As a result of these researches, it was seen that intensive researches were carried out especially on the essential oils of *Origanum* species and when the essential oil was evaluated phytochemically, it was seen that it contains especially carvacrol and thymol compounds as the main components. In addition, it was revealed that both the essential oil and extracts of this species have significant antidiabetic and anticancer effects when used both directly and in nanoparticles. *Origanum* species, which people are quite familiar with due to its safe use as a spice and tea by the public for many years, has shown that it can be promisingly effective on human health, including diabetes and cancer, with recent studies on it.

Keywords: *Origanum* species, phytochemicals, antidiabetic activity, anticancer activity

ÖZET

Kanser ve diyabet, dünya genelinde insanlarda en sık görülen kronik hastalıklardan ikisidir. Özellikle gelişmekte olan ülkeler, bu hastalıkların tedavisinde destekleyici veya tamamlayıcı tedavi olarak bitkilere güvenmeye devam etmektedir. Bu çalışmanın amacı, baharat ve çay olarak güvenle kullanılan ve Türkiye için önemli cinslerden biri olan *Origanum* cinsinin fitokimyasal içeriği ile antidiyabetik ve antikanser etkileri üzerine yapılan çalışmaları derlemek ve bu türün sağlık açısından önemini ortaya koymaktır. Bu amaçla ScienceDirect, Springer, Wiley Online Library, Web of Science, Taylor & Francis, Google Scholar gibi önemli veri tabanları taranmıştır. Bu araştırmalar sonucunda özellikle *Origanum* türlerinin uçucu yağları üzerinde yoğun araştırmalar yapıldığı görülmüş ve uçucu yağ fitokimyasal olarak değerlendirildiğinde ana bileşen olarak özellikle karvakrol ve timol bileşiklerini içerdiği görülmüştür. Ayrıca bu türün hem uçucu yağının hem de ekstraktlarının, hem doğrudan hem de nanopartiküller içinde kullanıldığında önemli antidiyabetik ve antikanser etkilere sahip olduğu ortaya konmuştur. Uzun yıllardır halk tarafından baharat ve çay olarak güvenli bir şekilde kullanılması nedeniyle insanların oldukça aşina olduğu *Origanum* türleri üzerinde yapılan son çalışmalar, bu türlerin diyabet ve kanser de dahil olmak üzere insan sağlığı üzerinde umut verici bir şekilde etkili olabileceğini göstermiştir.

Anahtar kelimeler: *Origanum* türleri, fitokimyasallar, antidiyabetik aktivite, antikanser aktivite

***Correspondence:**
ali.sen@marmara.edu.tr
alisenfb@yahoo.com

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Introduction

The first interest of man in plants began by the need for food, shelter and protection, but later on, attention in this regard turned to seeking remedies for injuries and diseases.

Lamiaceae is one of the families containing the most important plant species used for medicinal purposes from ancient times to the present day. This family is the sixth largest Angiosperm with more than 245 genera and 7886 species and is spread all over the world. Many species of this family are very important in economic and medical terms (Selvi et al., 2022).

One of the most economically important of the Lamiaceae family is the genus *Origanum*. This plant can be annual, perennial and shrubby. It is quite widespread worldwide. It is used as a flavoring, ornamental and spice (Zhou et al., 2021). *Origanum* species has been described by a wide range of chemical and morphological and diversity (Padulosi et al., 1997).

Each species in the genus *Origanum* have an erect, medium-thick stem and spotted glands, ±ovate leaves, are annual or perennial semi-bushy. Flowers on vertical laster (semi) sessile. Verticillaster in dense spikes with distinct, colored bracts. Slightly paniculate and inflorescences, Calyxes straight and very variable: Regularly 5-toothed, 2 or 1-lipped for 9/10 to 1/5; tubular, campanulate or flat; throats may or may not be hairy. Corollas variable: 2-lipped for 2/5 to 1/7, may or may not be humped (vesicular), sometimes flattened; straight tubular or slightly curved. Stamens equal or unequal in length; ascending, straight or separated, widely ridged (Ietswaart et al., 1980).

The current survey of the genus *Origanum* has been identified 10 sections so far: Prolaticorolla Amaracus, Campanulaticalyx, Brevifilamentum, Longitubus, Chilocalyx, Majorana, Elongatispica, Origanum and Anatolicon. There are 38 known species, one by 6 subspecies and the other with 3 species. Also, 17 taxa of hybrid origin have been identified (Ietswaart et al., 1980). Most of this genus is very locally distributed around the Mediterranean (Padulosi et al., 1997).

Metabolites (primary and secondary) formed by plants have a wide range of functions. Secondary metabolites have been used for beneficial roles in humans. At the same time, essential oils and their components are also used for potential multipurpose functions (Chishti et al., 2013).

Volatile oils are abundant in plants belonging to the genus *Origanum* (Zhou et al., 2021). *Origanum* essential oils consist of a number of main components that play a role in the various plant scents (Padulosi et al., 1997). Terpenoids such as carvacrol, thymol, carbamen and terpirenol are the main components of the essential oil of this genus. 92 compounds such as monoterpenes, sesquiterpenoids and other derivatives are the compounds found in these essential oils to date. The non-volatile components of genus *Origanum* such as flavonoids, triterpenes and organic acids have rarely been studied (Zhou et al., 2021). The essential oils of members of the *Origanum* genus vary in both the total quantity and the qualitative composition produced by the plants. Even a single *Origanum* species, such as *O. vulgare*, which is quite common and widely used, contains a wide chemical diversity (Padulosi et al., 1997). Different parts of plants and roots of plants change the composition and content of essential oils (Zhou et al., 2021). The geographical distribution or the time of collection of the plant determines the qualitative and quantitative variation of essential oils in species (Padulosi et al., 1997).

1. Traditional uses of the genus *Origanum*

Medicinal and aromatic plants are important for biological processes because some populations can achieve their primary health care from these plants (Chishti et al., 2013). *Origanum* species have a curative value in hypoglycemic treatments and have been used for a long time as local medicines in traditional medicine and spices and in purification rituals (Kintzios et al., 2002). Antispasmodic, antitumoral and analgesic are the reported activities of *Origanu*m spp., and its activities also include antifungal, antimicrobial, insecticidal and antioxidant activities. *Origanum* species are used in Turkish folk medicine for expectorant, antiparasitic, antihemontic and gastrointestinal complaints. The Genus *Origanum* is beneficial in the healing process of stomach ulcers. Some of the uses of *Origanum* spp. are as a carminative, sudorific, stimulant and tonic. It is also used as a folk remedy against colic, cough, toothache and irregular menstrual cycles. *Origanum* spp. is also a very effective disinfectant. It is used as a spice in all cuisines of the world to add flavor to foods. It is used in long-term treatments to prevent diabetes complications. It has an anti-inflammatory effect and its potential is promising (Chishti et al., 2013)

Iranian Medicine uses *O. vulgare* ssp. *viride* (Boiss.) as a stomachic, antitussive, antineuralgic, expectorant and diuretic. *O. dubium* Boiss. is widespread in Southern Türkiye, Greece, and Cyprus. It is used externally as an antirheumatic by the public in Cyprus. *Origanum hypericifolium* O. Schwarz and P.H. Davis is an species endemic to Türkiye and is used as a medicinal herbal tea in Türkiye for stomach complaints, colds and weakness.

Origanum sipyleum L. has traditional use for the treatment of gastrointestinal disorders and cough. Origani vulgaris herba has been used as an expectorant and spasmolytic agent in respiratory diseases, gastrointestinal diseases (such as bile expectorant, digestive, spasmolytic), oral antiseptic, diuretic and antiseptic, and in dermatological disorders.

2. Phytochemical constituents of the genus *Origanum*

Identification of *O. compactum* volatile components was performed using GC-MS analysis. The essential oil of *O. compactum* is mainly represented by oxygenated monoterpenes with 80.7%, while monoterpene hydrocarbons with 8.24%, oxygenated sesquiterpenes with 5.34% and sesquiterpene hydrocarbons with 3.37% occur in the lowest percentage. The major components identified were 54.6% thymol, 23.18% carvacrol and 7.12% *p*-cymene (Assaggaf et al., 2023).

LC-MS/MS results showed the presence of 12 polyphenolic compounds in *O. majorana* and 6 in *O. vulgare*. *O. majorana* contains caffeic acid, carnosic acid, cinnamic acid, chlorogenic acid, eugenol, ferulic acid, gallic acid, p-coumaric acid, pyrogallol, resorcinol, rosmarinic acid and syringic acid. Chicoric acid, chlorogenic acid, ferulic acid, gentic acid, rosmarinic acid and salvianolic acid B were found in *O. vulgare* (Perez Gutierrez et al., 2022).

A study indicated that the main component of *Origanum onites* L. essential oil was carvacrol (CV, phenolic monoterpene) with 72% and the other components were 7.6% thymol (phenolic monoterpene), 7.3% *p*-cymene (monocyclic monoterpene), 3.8% linalool (acyclic monoterpene), 2.0% *β*-bisabolene (sesquiterpene), 1.8% terpinen-4-ol (monocyclic monoterpene), 1.1% borneol (bicyclic monoterpene), 0.7% *β*-caryophyllene (sesquiterpene), 0.7% γ-terpinene (monocyclic monoterpene), 0.6% α-terpinene (monocyclic monoterpene) and 0.5% α-terpineol (monocyclic monoterpene) (Tomsuk et al., 2024).

Sökmen et al. evaluated the essential oil obtained by hydrodistillation from the leaves of the *Origanum minutiflorum* in terms of yield and chemical components (by GC-MS and GC-FID analyses); and revealed that the yield was 3.1% (v/w), the volatile oil contained 64 compounds, carvacrol was the predominant compound with a rate of 64.29%, followed by *p*-cymene with a rate of 9.56% (Sökmen et al., 2020).

Yusuf et al. analyzed the aqueous extract of *O. vulgare* (OV) using gas chromatography-mass spectrometry (GC-MS) and revealed the presence of 13 bioactive compounds. The main compounds among these compounds were determined to be hexadecanoic acid, methyl ester with 24.71%, 9-octadecenoic acid (Z)-, methyl ester with 22.52%, methyl stearate with 15.40% and 9-octadecenoic acid (Z)-methyl ester with 11.56% (Yusuf et al., 2023).

Erenler et al. identified the compounds of *O. vulgare* essential oil (OVEO) were by GC-MS analysis, and OVEO was found to contain carvacrol (90.4%) as the major compound (Erenler et al., 2021).

3. Biological activity

3.1. Antidiabetic activity

Chronic Diabetes occurs when the pancreas does not produce enough insulin or when the body cannot use the insulin it produces effectively. The function of the insulin hormone is to regulate blood sugar. High blood sugar or increased blood sugar is hyperglycemia and is a prominent and common effect of uncontrolled diabetes. Over time, diabetes causes serious damage to many systems in the body, primarily nerve cells and blood vessels (WHO, n.d.). Increased glucose concentrations in venous plasma or increased A1C in the blood are indicators of the presence of diabetes. Diabetes is typically divided into several clinical categories, but these are tested repeatedly based on metabolomics, genetics, and other criteria and pathophysiology. Diabetes is generally classified as follows: 1. Type 1 diabetes; 2. Type 2 diabetes; 3. Gestational diabetes mellitus; 4. There are also specific types of diabetes due to other causes, such as monogenic diabetes syndromes, exocrine pancreas diseases, and drug or chemical-induced diabetes (ElSayed et al., 2024).

Insulin injection and hypoglycemic agents are basic and effective drugs for the treatment of diabetes mellitus, but they have some side effects and do not affect diabetes complications in the long term. Effective compounds by fewer side effects are absolutely necessary for the treatment of diabetes. Medicinal plants have long been used as alternative or complementary treatments for these and other diseases. Herbal medicines are widely prescribed to patients all over the world due to their availability, low cost, low side effects, and also their effectiveness. (Bahmani et al., 2014). Effects on glucose uptake and glucose transporters, inhibition of α-glucosidase and α-amylase, inhibition of protein tyrosine phosphatase 1B activity, enhancement of insulin secretion and pancreatic β-cell proliferation and antioxidant activity are possible mechanisms of action of natural products in diabetes (Governa et al., 2018).

In a study, the inhibitory effects of *Origanum compactum* and *Origanum elongatum* extracts on α-glucosidase and α-amylase activity were evaluated under controlled

conditions. As a result of the evaluation, they showed significant dose-dependent inhibition. According to the results, aqueous extracts showed significant inhibitory effects against both enzymes, even outperforming the reference inhibitor acarbose. *O. compactum* and *O. elongatum* extracts exhibited effective inhibitory activity against α-amylase with an EC_{50} value of 128.13 and 162.81 µg/mL, respectively. As the concentration of acarbose used as standard, a gradual increase in inhibitory activity was observed. The EC_{50} values of *O. compactum* and *O. elongatum* extracts for inhibition of α-glucosidase secretion were found to be 14.28 and 14.70 µg/mL, respectively, which were equivalent and comparable to standard acarbose (EC_{50} value: 17.27 µg/mL). Moreover, in healthy rats, *ex vivo* oral glucose tolerance test (OGTT) was carried out and the capacity of the extract to reduce elevated blood glucose levels after high glucose load was evaluated. Rats receiving *Origanum compactum* and *Origanum longatum* extracts and oral antidiabetic drug glibenclamide showed significant positive antihyperglycemic responses compared to rats in the control group, which were given pre-distilled water. The extracts administered orally at a dose of 400 mg/kg successfully reduced postprandial hyperglycemia when taken 30 minutes before glucose overload. On the other hand, glibenclamide effectively suppressed the increase in postprandial blood glucose levels during the first hour (60 minutes) after glucose consumption, and the blood glucose levels were significantly reduced. The results indicate that the boiled extracts of the tested oregano species possess remarkable antihyperglycemic effects comparable to glibenclamide, a widely used antidiabetic drug in clinical practice (Al Kamaly et al., 2024).

In another study, the antidiabetic potential of *Origanum compacta* essential oil (OCEO) was evaluated using α-glucosidase and α-amylase enzymes. The results show that OCEO exhibits significant ability to inhibit pancreatic α-glucosidase and α-amylase *in vitro*. Experimental evaluations revealed higher IC_{50} values (120 µg/mL for α-glucosidase; 150 µg/mL for α-amylase) of OCEO compared to the control drug acarbose. It can be said that the antidiabetic activity of essential oils is based on various bioactive compounds. Numerous studies have reported that carvacrol and thymol exhibited antidiabetic properties in both *in vivo* and *in vitro* experiments. In an *in silico* study investigating the effect of essential oil components (carvacrol and thymol) on human NADPH oxidase, it was found that the essential oil components showed good binding affinity, and carvacrol and thymol also showed good binding affinity towards lysosomal acid alpha-glucosidase and salivary amylase. The researchers suggested that these results indicate that *O. compactum* essential oil-based diabetes treatment may have translational potential (Assaggaf et al., 2023).

In another experimentation, evaluated streptozotocin (STZ) induced diabetics rats and aimed to reveal the protective effect of *Origanum onites* L. against possible changes in these parameters. *Origanum onites* L. extract was administered intraperitoneally to these sera at a dose of 50 mg/kg per day for 6 weeks and serum creatinine, ALT, AST and inflammatory cytokine levels were measured biochemically. Malondialdehyde (MDA) and glutathione (GSH) levels were also measured in liver tissues. ALT, AST, creatinine and MDA levels increased in the DM group, whereas a significant decrease was observed in the treatment group. GSH levels decreased in the DM group, whereas there was a significant increase in the opposite direction in the *Origanum onites* group. When plasma cytokine levels were analyzed, an increase was observed in the DM group, while a significant decrease was observed in the *Origanum onites* group. These results revealed that *Origanum onites* L. has a protective effect against the complications that may occur in DM by preventing inflammation and oxidative damage. At the end of the study, the diabetic rats had lost 40% of their body weight, while the *Origanum onites*-treated diabetics lost only 12%. After 3 weeks, a 6% decrease in blood glucose levels was observed in the *Origanum onites*-treated group, while there was no change in blood glucose levels in the untreated group (Aydemir et al., 2022).

In another experiment, according to the glucose tolerance test, *Origanum grosii* extract at a dose of 150 mg/kg significantly suppressed the level of postprandial hyperglycemia compared to the normal control group. This species has an antihyperglycemic effect. This may be due to the presence of a large family of hypoglycemic chemicals such as flavonoids, terpenes, and tannins found in *Origanum grosii*. These components improve the functioning of pancreatic tissue by increasing insulin secretion or reducing glucose absorption from the intestine. In addition, the antihyperglycemic effect of this herb may be partly explained by the inhibition of α-amylase or other enzymes. The antienzymatic activity of this species is likely due to its phenolic content. It showed that the leaves had high concentrations of trace elements (Ca, Mg and K) and a complete absence of heavy metals (Cr, Ni and B), which were present in small quantities. The chemical families of the oregano plant may act individually or synergistically to cause the hypoglycemic effect of this genus (El Hassouni et al., 2021).

In another study, it has been established that exposure to chronic immobilization stress promotes an increase in fasting glucose levels and the development of hyperglycemia. Immobilization stress leads to impaired

stomatal functions of the endocrine, cardiovascular and immune systems characterized by hyperlipidemia and hyperglycemia, as well as impairment of some biochemical parameters such as total creatinine, protein and urea. The hypoglycemic effect of *O. vulgare* aqueous extract was evaluated in rabbits with hyperglycemia model for 21 days. During the treatment, an oral glucose tolerance test (OGTT) was performed. Oral administration of aqueous extracts showed a significant effect on improving glucose tolerance and hyperglycemia. In addition, *O. vulgare* extract decreased LDL cholesterol and total cholesterol, conversely, increased HDL cholesterol, and also decreased liver enzymes (ALT and AST) compared to the untreated group (Aghajanyan & Tadevosyan, 2022).

In different study, the ultrasonic extraction options of polyphenolic compounds from the combination of *Cinnamomum verum* (CV), *Origanum majora* (OM) and *Origanum vulgare* (OV) and their potential antidiabetic activities against glucose-induced diabetes activity were investigated. Diabetic zebrafish were studied. Hyperglycemic fish showed elevated triglyceride and cholesterol levels, while the extracts completely blocked these metabolic changes. The combination of the three herbs showed a higher antidiabetic effect than CV, OM and OV, suggesting a synergistic effect between them. Extracts of CV, CM, OV and COV (a mixture of three extracts) showed antidiabetic effects probably due to their phenolic compounds. The results indicate that supplementation by a combination of three herbs can reduce diabetic complications. The ability to suppress glycemia and lipid profile after treatment with the polyherbal formulation was confirmed in our zebrafish model of T2DM. (Perez Gutierrez et al., 2022)

In another experiment, the development of inhibitors of advanced glycation end products (AGEs) is considered to have therapeutic potential in diabetic patients. *Origanum majorana* (OM) and glibenclamide were administered to streptozotocin-induced diabetic mice for 28 days and were found to have beneficial effects on glucose levels and renal metabolic abnormalities including AGE formation. OM also had a significant effect on AGE formation *in vitro*, and its glycation inhibitory activity was found to be more effective than that obtained using aminoguanidine as a standard antiglycation agent. The antiglycation activity of OM is partly attributed to its antioxidant activity and its ability to scavenge reactive carbonyls. OM alleviated oxidative stress in diabetic conditions by inhibiting lipid peroxidation, preventing and/or delaying the onset of renal injury. OM treatment improved diabetes control and these parameters compared to glibenclamide. These results suggest that OM may prevent or alleviate AGE-related chronic diseases (Perez Gutierrez et al., 2012).

In a study investigating the protective role of *Origanum majorana* L. on biochemical parameters of STZ-induced rats, diabetic rats were divided into two groups; the first group received no treatment, while the second group was administered *Origanum majorana* L. extract (200 mg/kg) for 6 weeks, and serum alanine aminotransferase (ALT), creatinine, and aminotransferase (AST) values were measured. In addition, GSH and MDA levels were measured in liver and kidney tissues. It was found that creatinine, ALT and AST values increased in diabetic rats and decreased significantly in the treatment group administered *Origanum majorana* extract. While GSH values decreased in diabetic rats, conversely, MDA levels increased. It was observed that treatment with *Origanum majorana* extract reduced lipid peroxidation and caused a significant increase in GSH levels. As a result, the researchers concluded that treatment with *Origanum majorana* extract has a protective effect against diabetic nephropathy by preventing oxidative damage. STZ-induced DM is known to be associated with significant weight loss and increased blood sugar levels. At the end of the study, it was determined that the body weight of the rats in the OM treatment group increased significantly compared to the DM group. It was also observed that the blood glucose levels in the OM-treated rats decreased significantly compared to the DM group (Çakar et al., 2023).

In another experiment, medicinal plants and green silver nanoparticle production (AgNP) are effective treatments for diabetes. Evaluation of antidiabetic and liver-protective effects of *Origanum majorana* leaf extract (OMLE) and nanoparticles (OMLENP) in STZ-induced diabetes in rats. The rats were divided into 5 groups: Group I: non-diabetic control, Group II: streptozotoSTZ administered; Group III: Diabetic rats were administered with glibenclamide, Group IV: Diabetic rats were administered with OMLE, Group V: Diabetic rats were administered with OMLENP. Various parameters were evaluated. Both OMLE and OMLENP significantly reduced blood glucose levels compared to the untreated diabetic group. Diabetics treated with glibenclamide and diabetics treated with OMLE or OMLENP had lower TG and TC levels compared to the diabetic group showed a significant decrease in the levels. Compared with the extract, OMLENP treatment showed superior effect in improving insulin sensitivity, lipid profile, antioxidant functions and liver functions. Histopathological examination showed that OMLE and OMLENP alleviated STZ-induced liver tissue injury with significant reduction in inflammatory infiltrates and cellular degeneration. OMLE and OMLENP exhibit potential antidiabetic and liver protective effects with enhanced efficacy possibly due to improved bioavailability (Rateb et al., 2024).

Elghazaly et al. evaluated the ameliorative and antihyperglycemic effects of *O. majora*na leaf extract (OMLE) on the spleen tissue of diabetic rats. Blood glucose and insulin levels, catalase (CAT) and superoxide dismutase (SOD) activities, GSH and MDA levels, and white blood cell (WBC) counts were measured. Spleen tissues were examined histologically. In diabetic patients, there was a significant increase in blood glucose and MDA levels, and a significant decrease in plasma insulin levels, SOD and CAT activities, white blood cell counts, and GSH levels. Treatment of diabetic rats with OMLE improved glucose, insulin, and white blood cell counts. There was a significant increase in antioxidant enzyme activities when diabetic rats were treated with OMLE. The results showed that there were many histological changes in the spleen tissues of diabetic rats. The biochemical indices and histological structure were significantly improved when diabetic rats were treated with OMLE. OMLE can have a protective effect on spleen problems in diabetic rats and reduce the complications of diabetes (Elghazaly et al., 2023).

Oregano majorana extract (OME) was incorporated into nanoscale systems to enhance its biological effects at low doses. Optimal nano-cubosomal (NC) systems were selected and evaluated *in vivo* to compare their effects with conventional OME in streptozotocin-induced diabetic patients. The results showed that OME was effective in reducing blood glucose levels and attenuating molecular and histopathological changes in the submandibular salivary glands in diabetes due to its antihyperglycemic, anti-inflammatory and antioxidant effects. Furthermore, the biological activity of the extract was shown to be enhanced when incorporated into NC systems even at lower doses. Therefore, it is possible that cubosomal nanosystems can be considered as potential carriers to achieve the best result with OME (Farag et al., 2022).

In another experiment has evaluated the antidiabetic activity of the oral aqueous extract of *Origanum floribundum* daily for 28 days using alloxan as a diabetes inducing agent. Blood glucose levels were significantly elevated in untreated alloxan-induced diabetics compared to untreated normal rats. The aqueous extract of the leaves at doses of 200 and 400 mg/kg exhibited significant antihyperglycemic activity and caused a decrease in blood glucose levels. The findings showed that various secondary metabolites such as flavonoids, alkaloids, saponins, terpenoids, polyphenols, tannins, sterols, and coumarins were found in the extract. The hypoglycemic effect of the aqueous extract is due to its components: polyphenols from these secondary metabolites, especially flavonoids, have been proposed as the best therapeutic agents in the treatment of diabetes mellitus and its chronic complications. Moreover, natural ingredients may act individually or synergistically to produce a hypoglycemic effect (M'hamed Nasri et al., 2020).

3.2. Anticancer activity

Cancer is a large group of diseases that can begin in virtually any organ or tissue of the body in which abnormal cells grow uncontrollably, expand beyond their normal boundaries, penetrate into adjacent areas of the body and spread into other organs. The latter process is called metastasis and is one of the leading causes of cancer-related deaths. Neoplasm and malignancy are other common names for cancer (WHO, n.d.).

Cancer is the result of genetic and epigenetic changes in the stem cells (progenitors) of certain cell types. Two distinct categories of genes are involved in carcinogenesis. Oncogenes are activated proto-oncogenes, whereas tumor suppressor genes are globally inactivated by mutations, point mutations, deletions, rearrangements, and duplications. Both types of genes are required for normal cell proliferation and differentiation, and abnormal expression leads to abnormal cell proliferation. When this situation is systematically disrupted, cancer occurs (Spandidos, 2007).

In addition, cancer is one of the most feared diseases of the 20th century and continues to spread more and more in the 21st century. The situation is so alarming that every fourth person is at risk of developing cancer during their lifetime (Roy & Saikia, 2016).

The most common cancers in men are colorectal, liver, lung, prostate and stomach cancers; and in women breast, cervical, colorectal, lung and thyroid cancers (WHO, n.d.).

Although effective cancer treatments are still awaiting, some unconventional treatments such as surgery, radiotherapy and chemotherapy and some advanced technologies such as stem cell therapy, gene therapy, natural antioxidants, nanoparticles, photodynamic therapy, targeted therapy and precision medicine are used to diagnose cancer and are available for treatment (Kaur et al., 2023).

Today, the active ingredients of many drugs used in cancer treatment are derived from natural sources. A large part of these natural resources are plants, which are capable of synthesizing a wide variety of chemicals. Plant chemicals exert their anticancer effects through mechanisms such as inactivation of carcinogens, antiproliferation, cell cycle arrest, induction of apoptosis and differentiation, suppression of angiogenesis, antioxidant effects, and reduction of multidrug resistance. In recent years, the number of studies on cancer treatment with medicinal

herbs has increased worldwide. In this case, ethnobotanical knowledge, passed down from the depths of centuries to the present day, comes to the fore, and the use of medicinal plants becomes important (Bozyel et al., 2019).

In a study, the DNA synthesis inhibitory and antiproliferative effects of *Origanum onites* L. essential oil (EOOO) and carvacrol (CV), one of the most important components in its essential oil, were demonstrated on the hepatocellular carcinoma cell line HepG2. HepG2 cells were treated with EOOO and CV for 48 hours and then the DNA synthesis level was evaluated by BrdU incorporation test. As a result, a decline in DNA damage in HepG2 cancer cell lines was observed as EOOO and CV increased. DNA synthesis was significantly decreased in cells by EOOO applied at a concentration of 0.06 µg/mL compared to vehicle-treated control cells. It was found that EOOO applied at a concentration of 0.08 µg/ml had an inhibition rate of DNA synthesis of approximately 50%. Compared to solvent-treated control cells, DNA synthesis in cells was significantly decreased in a concentration-dependent manner at CV at a concentration of 60 µg/mL. EOOO and CV were found to inhibit HepG2 cell proliferation. Cell viability was determined using trypan blue exclusion (TB) test after incubation with EOOO and CV. The number of viable cells decreased in a time- and concentration-dependent manner, similar to the results obtained using the BrdU test. After 48 h, the number of viable cells decreased to 65% and 51% with EOOO applied at concentrations of 0.08 and 0.09 µg/mL, respectively. In addition, the number of viable cells was significantly reduced to 39% after 72 h with EOOO applied at a concentration of 0.09 µg/mL. The IC_{50} value of EOOO at 24 and 48 h was calculated as 0.09 µg/mL. CV was also found to be cytotoxic to HepG2 cells, similar to the effect of EOOO. Compared to vehicle-treated control cells, the number of cells was significantly decreased with CV applied at a concentration of 45 and 75 µg/mL. When applied at a concentration of 75 µg/ml, CV reduced cell viability to 64% and 45% at 24 and 48 hours, respectively, and when applied at a concentration of 45 µg/ml, it reduced cell viability to 54% at 72 hours and 50% at 96 hours. The CV IC_{50} values were revealed to be 75 µg/mL for the 48th hour and 45 µg/mL for the 72nd and 96th hours (Tomsuk et al., 2024).

Carvacrol has been reported to be the main component of essential oils of aromatic medicinal plants belonging to the Lamiaceae family, such as *Origanum vulgare* and *Thymus vulgaris*. Chemically, it is a phenolic monoterpenoid known as 5-isopropyl-2-methylphenol. The researchers proposed that the current research is directed towards identifying carvacrol, a potent compound with various pharmacological activities such as antioxidant, anticancer and anti-inflammatory. Carvacrol has been found to exhibit potent cytotoxic activities against various carcinoma cell lines by inducing apoptosis through the action of numerous proteins related to the apoptotic pathway, the PI3K/Akt pathway, and the MAPK pathway. In addition to the apoptotic pathway, carvacrol has also been shown to exhibit cytotoxic activity against some cancer cells. Carvacrol has been shown to exhibit potent anticancer activity against various carcinoma cell lines by inhibiting cell proliferation through the apoptotic pathway triggered by activation of caspases and increased DNA fragmentation. It also showed protective activity against H_2O_2-induced DNA damage (Mondal et al., 2020).

In another study, the cytotoxic effects of essential oils obtained from wild and cultivated forms of *Origanum acutidens* against A549 and H1299 lung cancer cells were investigated using MTT and CellTiter-Blue® Cell Viability assays. In the MTT experiment, the IC_{50} values of the essential oil obtained from the wild form of *O. acutidens* species against H1299 cells were calculated as 179, 157 and 132 µg/mL after 24, 48 and 72 hours, respectively. With rezazurin-based analysis, the IC_{50} values of *O. acutidens* wild form essential oil on H1299 cells after 24, 48 and 72 hours were determined as 150, 131 and 110 µg/mL. Using the MTT test, the IC_{50} values of the essential oil obtained from the wild form of *O. acutidens* against A549 cells after 24, 48 and 72 hours were found to be 118, 99 and 69 µg/mL, respectively. The cytotoxic effect of the essential oil obtained from the wild form of *O. acutidens* against A549 cells was evaluated using rezazurin-based assay and the essential oil was calculated to have 98, 83 and 57 µg/mL IC_{50} values after 24, 48 and 72 hours. It was observed that essential oils obtained from cultured and wild *O. acutidens* increased malondialdehyde levels in both A549 and H1299 cells. It was revealed that the highest membrane damage was seen in A549 cells treated with wild *O. acutidens* essential oil (Gökhan et al., 2021).

In another experiment, researchers tested the *in vitro* anticancer effects of ethanol extract obtained from *O. syriacum* (OSEE) against MDA-MB-231 cell line, an aggressive and highly metastatic human triple negative BC (TNBC) cell line, and the possible underlying mechanisms of action were investigated. The results showed that *O. syriacum* ethanol extract (OSEE) exerted potent anticancer and antimetastatic effects on aggressive TNBC phenotype by regulating cell adhesion, migration, invasion and angiogenesis processes via inhibition of STAT3 signaling as well as activation of p38 MAPK signaling pathways. OSEE not only induced cell cycle arrest in MDA-MB-231 cells, but also inhibited angiogenesis as well as activated apoptosis. *Origanum syriacum* contains multiple primary and

secondary bioactive metabolites. The study confirmed the presence of different classes of phytochemical compounds in *O. syriacum* ethanol extract (OSEE). OSEE contains cardiac glycosides, essential oils, flavonoids, phenols, quinones, steroids, tannins and terpenoids. Many of the bioactive compounds found in *O. syriacum* have been reported to have potent anti-breast cancer activities. Carvacrol, thymol, apigenin, naringenin, rosmarinic acid and thymoquinone have been reported to reduce the malignant phenotype of breast cancer (Mesmar et al., 2022).

The anticancer activity of different concentrations of *Origanum minutiflorum* essential oil was proven on A-549 (human lung cancer cell line), MCF-7 (human breastcancer cell line) and HepG2 (human hepatocellular carcinoma cell line). All the tested concentrations of the oil showed significant scolicidal activity against protoscolecium hydatid cysts. The results showed a concentration-dependent decrease in the viability of A-549, HepG2 and MCF-7 cells after exposure to *Origanum minutiflorum* oil for 24 hours. IC_{50} for HepG2, A-549 and MCF-7 cells were 0.028457%, 0.028682% and 0.0349235%, respectively. It was found that the anticancer activity of *O. minutiflorum* essential oil was more in HepG2 cells followed by MCF-7 and A-549 cells (Sökmen et al., 2020).

In a different study, it was investigated the anticancer potential of *Origanum majorana* leaf acetone extract (OMAE) against human colon cancer cells HT-29. The cytotoxic effect of OMAE, which was investigated by MTT test, was revealed by the researchers to have a significant inhibitory effect on the growth of HT-29 cells from a concentration of 1000 µg/mL to 62.5 µg/mL. It was observed that these inhibitory effects continued slightly up to a concentration of 31.25 µg/mL, and the IC_{50} of OMAE was stated to be at a concentration of 90 µg/mL. After the IC_{50} of OMAE was found, real-time RT-PCR was used to quantitatively analyze p53 expression after *in vitro* treatment of HT-29 cells with this IC_{50} dose. The results showed that the expression of p53 mRNA increased by 5.44-fold compared to the control cells. The apoptotic effect of OMAE was evaluated using annexin V staining. The extract induced cell apoptosis, with the number of apoptotic cells significantly increased (11.74%) in treated cells compared to untreated cells (0.73%). This increase in the percentage of apoptotic cells (treated) was almost the same in the early (5.92%) and late (5.82%) stages. Therefore, it was inferred that OMAE had an apoptotic effect rather than a necrotic effect (Ibrahim et al., 2022).

Since 2004, the World Health Organization has endorsed the use of alternative therapies as adjuvant therapies based on evidence of their benefits. Since then, some natural alternatives for treatment of cancer have been examined, including Oregano (Ov) and one of its main compound, carvacrol (Crv). Rojo-Ruvalcaba et al. also evaluated the cytotoxic effect of Ov and Crv on TN BC cell line (HCC-70). The lethal dose 50 was determined on the control HaCaT cell line using MTT assay with stimulation of Ov and Crv at different doses and concentrations. The found dose was used on the HCC-70 cell line. It was found that Ov reduced proliferation by 94.05 ± 0.11% and Crv by 93.43 ± 0.21%. This showed that Ov and Crv have strong cytotoxic effect to the HCC-70 cell line (Rojo-Ruvalcaba et al., 2020).

In another study, MTT assay was performed to determine the effect of *Origanum vulgare* extract on the viability of Molt-4 cells showed that *O. vulgare* extract reduced the viability of Molt-4 cells in a time- and dose-dependent manner. MTT assay showed that *O. vulgare* extract eliminated half of the Molt-4 cells after 72 hours at a concentration of 457 µg/mL. Expression of apoptotic pathway genes after treatment with *O. vulgare* extract, Bax and Bcl-2 gene expression were assessed after Molt-4 cells were treated with 1/5 IC_{50} of *O. vulgare* extract for 72 hours. *O. vulgare* extract induced the expression of the apoptotic gene Bax, while the expression of the anti-apoptotic gene Bcl-2 was decreased. Moreover, the expression of the gene Nrf2 was increased by *O. vulgare* extract. *O. vulgare* extract not only induced early or late apoptosis, but also increased necrosis in Molt-4 cells (Solouki et al., 2021).

Yusuf et al. investigated the cytotoxic potential of *O. vulgare* (OV) was evaluated as a potential source of natural products in the treatment of cervical cancer. Crude extracts and fractions were exposed to a cervical cancer cell line (HeLa) using the MTT assay. The potentials of the OV fractions, n-hexane, DCM, ethyl acetate and aqueous solutions were 57.95, 61.63, 172.4 and 176 µg/mL, respectively. These results were compared to vincristine (standard) with a CC_{50} of 0.75 µg/mL. The n-hexane fraction of *O. vulgare* showed the highest anticervical effect (57.95 µg/mL), followed by the DCM fraction (61.63 µg/mL). Also, the results obtained have showed that the crude extract of *O. vulgare* had an IC_{50} value of 170.2 ± 0.11 µg/mL (Yusuf et al., 2023).

Gîrd et al. investigated the cytotoxic activity of freeze-dried extracts of *Origanum vul*gare (OV) against human osteosarcoma cell line MG-63. The effects of the analyzed dried extracts on, cell survival, cell morphology and cell proliferation were measured. The antiproliferative effect of OV dried extract was performed against osteosarcoma bone cell line MG-63 by MTT assay. The results of the MTT assay showed that osteosarcoma cells were sensitive to OV dried extract and the effect was prominent at concentrations of 500 µg/mL and 700 µg/mL compared to the control group. Cytotoxicity was evaluated using Live &

Dead and lactate dehydrogenase assays. Treatment of osteosarcoma cells with *Origanum vulg*are dried extracts presented a dose-dependent increase in LDH release. After treating MG-63 cancer cells with 700 µg/mL OV dried extract for 24 h, a significant release of LDH into the medium was observed compared to the control. However, no significant differences were found at other OV dried extract concentrations (100, 300, and 500 µg/mL) compared to untreated cells. Microscopic observations using Calcein-AM and EthD-1 confirmed the cytotoxic effect of the tested dried extracts at various concentrations. To further investigate the potential anticancer effects, it has been investigated the effect of the dried extracts on cells using caspase-3/7 and proliferating cell nuclear antigen (PCNA) expression assays. Cells were incubated with extracts in a range of concentrations (100-700 µg/mL) for 24 h. Concerning the effect of the analyzed dried extracts on caspase-3/7 activation, it has been observed a dose-dependent effect at an extract concentration of 300 µg/mL. PCNA expression in osteoblasts treated with OV dried extracts at all analyzed concentrations was similar to that in untreated cells. According to the results, apoptosis is one of the main mechanisms involved in the cytotoxic properties of the tested extracts. As the extracts were standardized for phenolic compounds (rich in phenolic carboxylic acids and flavones), it is likely that these are the major components involved in the cytotoxic effect (Gird et al., 2021).

The cytotoxic effects of *O. majorana* volatile oils against A-431 and A-549 cancer cell lines were tested by MTT and CellTiter-Blue® cell viability assays. In both assays, the cytotoxic effect was observed to increase in parallel with the concentration and incubation time in both A-549 and A-431 cells. According to the results of MTT, the IC_{50} values after 24, 48 and 72 hours of incubation of the oil, were 218, 187 and 140 µg/mL in A-431 cells and 266, 222 and 182 µg/mL in A-549 cancer cell lines, respectively. Moreover, the IC_{50} values of oil after 24, 48, and 72 hours of incubation with the oil were 243, 203, and 167 µg/mL in A-549 in the CellTiter-Blue® Cell Viability assay. In A-431 cells, after incubation of oil at similar time intervals, 182, 145 and 111 µg/mL IC_{50} values were detected, respectively. It was found that the volatile oil was more effective on A-431 cancer cell lines, (mutant p53) than on A-549 cancer cell lines (wild-type p53). To assess the effect of *O. majorana* essential oil on the cell membrane, lactate dehydrogenase (LDH) activity was measured; it is released from the cells into the medium and is an early indicator of apoptosis. The LDH activity in A-431 cells increased more than that in A-549 cells, and the activity of LDH in both A-549 and A-431 cancer cell lines was higher than that in the control group. The apoptosis-inducing potential of *O. majorana* oil was observed after treating A-549 and A-431 cancer cell lines, cells with *O. majorana* volatile oil for 24 hours. It was observed that the apoptotic effect of volatile oil in terms of increasing caspase-3/7 activity in A-549 cells was twice as high as the apoptotic effect of *O. majorana* volatile oil in A-431 cells (Gökhan et al., 2022).

The inhibitory effects of *O. majorana* essential oil and extract on cell proliferation were investigated in one normal cell line and four cancer cell lines. The anticancer effects of extract, essential oil, 5-fluorouracil (5-FU) and cisplatin were evaluated on the cancer cell lines Hep3B (hepatocellular carcinoma), A549 (human lung carcinoma), MCF7 (human breast adenocarcinoma), HT29 (human colon carcinoma), and normal cell lines FL (human amniotic cells). The cytotoxic effect and antiproliferative activity of the extract and essential oil were examined by MTT and LDH (lactate dehydrogenase) methods, respectively. The essential oil showed significant activity against the cancer cell lines MCF-7 (IC_{50}, 7.1 µg/mL), Hep3B (IC_{50}, 7.4 µg/mL) and A549 (IC_{50}, 27.2 µg/mL) compared with the standards. In addition, the extract showed significant activity against MCF-7 (IC_{50}, 10.8 µg/mL) and Hep3B (IC_{50}, 27.2 µg/mL) cell lines. When comparing the essential oil and the extract, it was found that the essential oil had a higher antiproliferative effect than the extract on Hep3B, A549 and MCF7 cell lines. In this study, the cytotoxic activity of the essential oil and extract on cell lines was measured using an LDH cytotoxicity kit, which is based on measuring the amount of cytoplasmic LDH, an indicator of membrane integrity. The extract and essential oil (17%) were not cytotoxic to FL cells, but were toxic to cancer cells. However, the essential oil has therapeutic efficacy since it is safe for FL cells only at IC_{50} concentrations and below. The results showed that the essential oil has a cytostatic effect on cells. The cytotoxic effect of the extract was found to be higher than that of the essential oil. It has been suggested that the activity of the essential oil may be due to the synergistic effect of other compounds as well as the high content of carvacrol (90.4%) in the essential oil (Erenler et al., 2021).

Silver nanoparticles are recognized as smart magnetic particles due to their small size and large adsorption surface area. Silver nanoparticles have revolutionized cancer treatment, with silver nanoparticles playing an important role in this field due to advances in nanotechnology. In a study conducted by Chao Qian et al., AgNPs derived from *Origanum majorana* (*Thymus majorana*) caused a decrease in the viability of human breast cancer cells (MCF-7). MTT assay revealed the anti-breast cancer properties of silver nanoparticles in MCF-7, T-47D, and SkBr3 cells. The results indicated that the viability of cancer cells decreased within 3 days as the concentration of nanoparticles increased. The activities of

AgNPs against MCF-7, T-47D and SkBr3 cell lines were calculated as IC_{50} values and these values were found to be 97, 186 and 180 µg/mL, respectively. It was revealed that these nanoparticles induced apoptosis through signal transducer and transcription pathway 3 and P53 activator. The presence of silver NPs was found to induce cell apoptosis through activation of the pro-apoptotic markers Bax and cleaved caspase-8, while down-regulating the anti-apoptotic marker Bcl-2. In addition, silver NPs both inhibited colony formation and showed high sensitivity in the electrochemical detection of hydrazine, a potential carcinogen, with a detection limit of 0.25 µM (Chao Qian et al., 2024).

Conclusions

Cancer and diabetes are among the most important chronic diseases. In the treatment of these diseases, in addition to conventional medicines, products of natural origin are used as supportive or complementary. The fact that *Origanum* species are used both as spices and herbal teas in the world and in our country under the name of thyme suggests that the use of these species may be safe. In this review study, it was observed that intensive studies have been carried out on the essential oils of *Origanum* species, and the major components of the oil are carvacrol and thymol. Antidiabetic and anticancer studies on *Origanum* species show that these species have the potential to be promising naturally derived agents as supportive or complementary therapies in the treatment of diabetes and cancer. In addition, with the nanotechnology developed in recent years, the increase in the number of studies investigating the effects of nanoparticles developed from the essential oil or extract of *Origanum* species against these diseases has shown that *Origanum* species are important.

Author contributions

Merve Nur Bay, Ali Şen: Collection and compilation of data, writing of the manuscript. Ali Şen, Leyla Bitiş: Review and editing of the manuscript. Ali Şen, Leyla Bitiş: Correction and analysis of chemical compounds. Merve Nur Bay, Ali Şen, Leyla Bitiş: Designing, supervising and editing of the manuscript. Merve Nur Bay, Ali Şen, Leyla Bitiş: All authors read and approved the final manuscript.

Declaration of interests

The authors declare that there is no conflict of interest.

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Phytochemistry and biological activities of the genus *Rubus*

Rubus cinsinin fitokimyası ve biyolojik aktiviteleri

Deniz Oylumlu, Ali Şen*

Department of Pharmacognosy, Faculty of Pharmacy, Marmara University, İstanbul, Türkiye

ABSTRACT

The genus *Rubus*, a member of the Rosaceae family, includes important species with both food and medicinal uses. With an emphasis on the anti-inflammatory, anti-cancer, antioxidant, and antibacterial properties of the main chemicals present in *Rubus* species, this review aims to synthesize the results of recent studies in order to better understand the biological activity and chemical composition of these species and their value as natural bioactive resources. This work also seeks to identify future directions for research that could enhance the clinical applications of *Rubus*-based bioactive compounds. For this purpose, NCBI, MDPI, ScienceDirect, Google Scholar, MEDLINE and Springer Nature Link databases were searched for recent articles on phytochemical and biological activity studies on *Rubus* species. The results showed that *Rubus* species are rich in compounds belonging to different chemical groups (phenolic acids, tannins, flavonoids, anthocyanins, etc.) and extracts and/or secondary metabolites of these species have important biological activities such as antioxidant, antimicrobial, anti-inflammatory, and anticancer effects.

Keywords: *Rubus* species, phytochemistry, biological activity

ÖZET

Rosaceae ailesinin bir üyesi olan *Rubus* cinsi, hem gıda hem de tıbbi kullanımları olan önemli türleri içerir. Bu derleme, *Rubus* türlerinde bulunan ana kimyasalların anti-inflamatuar, anti-kanser, antioksidan ve antibakteriyel özelliklerine vurgu yaparak, bu türlerin biyolojik aktivitesini, kimyasal bileşimini ve doğal biyoaktif kaynaklar olarak değerlerini daha iyi anlamak için son çalışmaların sonuçlarını analiz etmeyi amaçlamaktadır. Bu çalışma ayrıca *Rubus* bazlı biyoaktif bileşiklerin klinik uygulamalarını geliştirebilecek araştırmalar için bir rehber olma niteliğini amaçlamaktadır. Bu amaçla NCBI, MDPI, ScienceDirect, Google Scholar, MEDLINE ve Springer Nature Link veri tabanlarında *Rubus* türleri üzerinde yapılan fitokimyasal ve biyolojik aktivite çalışmalarını içeren güncel makaleler taranmıştır. Sonuçlar, *Rubus* türlerinin farklı kimyasal gruplara ait bileşikler (fenolik asitler, tanenler, flavonoidler, antosiyaninler, vb.) açısından zengin olduğunu ve bu türlerin ekstraktlarının ve/veya sekonder metabolitlerinin antioksidan, antimikrobiyal, anti-inflamatuar ve antikanser etkiler gibi önemli biyolojik aktivitelere sahip olduğunu göstermiştir.

Anahtar kelimeler: *Rubus* türleri, fitokimya, biyolojik aktivite

***Correspondence:**
ali.sen@marmara.edu.tr
alisenfb@yahoo.com

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0000-0002-2144-5741

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Introduction

Plants not only form the basis of many medicines used in the treatment of various diseases, but have also found their place in many fields from textile production to food and cosmetics (Bhatt et al., 2023). Through the experiences recorded from past generations to the present, plants have gained significant importance in our lives due to their therapeutic effects.

One of the existing plant species, *Rubus* species traditionally used worldwide for their food and medicinal properties. *Rubus* species belong to the Rosaceae family, with approximately 1,500 species worldwide. In Türkiye, 16 species grow naturally (Güner et al., 2012). The common ones are *Rubus idaeus, Rubus sanctus* and *Rubus saxatilis*. *Rubus* species are commonly known as 'blackberry, raspberry, wild grape'. Plants of this genus can spread from sea level to an altitude of 4500 meters (Bhuyan & Dutta, 2021).

Some of the plants belonging to this genus have woody stems with thorns, similar to roses. The leaves are mostly palmate or pedate compound, sometimes pinnate. The leaves are compound, consisting of 3 to 5 leaflets, with the central leaflet being the largest; leaf edges range from serrated to irregularly toothed. Small flowers, measuring 0.5-1.5 cm and varying in color from white to pink, begin to emerge in the second year after planting. The stipules are mostly narrow and they may be directly attached to the petiole. Most of the plants in this genus are perennial and they are shrubby plants. Except for *Rubus chamaemorus*, the majority of species are hermaphrodites, meaning that both male and female reproductive parts are present in the same flower. The color of the fruit varies from white to black. Fruits of many of the species in this genus are edible. In many countries, the fruit is primarily grown for fresh consumption. Processed *Rubus* fruit, on the other hand, is widely utilized in the food and beverage sectors to create products such as wine, beer, soft drinks, jam (Davis & Meikle, 1972).

Rubus species are adapted to very extreme conditions such as cold/hot climate conditions, and high altitude etc. (Wairegi et al., 2024). The phytochemicals found in plants of the *Rubus* genus, such as tannins, flavonoids, phenolic acids, terpenoids, anthocyanins, lignans and vitamins make this genus an important and ideal subject for scientific research. Numerous cultures, despite lacking awareness of the specific chemical compounds, have recognized the medicinal qualities of *Rubus* and utilized them in various applications owing to their significant nutritional and medicinal benefits.

Rubus species have been commonly utilized either on their own or as part of traditional Chinese and Indian medicine (Hummer, 2010). In Indian medicine, leaves and barks of *Rubus* species are used for its astringent and diuretic properties (Hummer, 2010). In traditional Chinese medicine, *Rubus* is utilized to strengthen and stabilize the kidneys, helping to conserve vital energy and treat liver and kidney deficiencies (Hummer, 2010).

It has been applied to enhance vision, reduce lower back pain, stop frequent urination or treat blurred vision, and prevent cancers of the uterus, cervix, and colon (Hummer, 2010). In ancient Greek, Hippocrates recommended applying stems and leaves of blackberries steeped in white wine as an astringent remedy to heal wounds and facilitate childbirth (Hummer, 2010).

The aim of this review is to compile recent phytochemical and biological activity studies on *Rubus* species by searching NCBI (National Center for Biotechnology Information), MDPI (Multidisciplinary Digital Publishing Institute), ScienceDirect, Google Scholar, MEDLINE and Springer Nature Link databases and to reveal the phytochemical richness and medicinal importance of the species belonging to this genus.

1. Phytochemistry of *Rubus* species

1.1. Anthocyanins

Anthocyanins are phenolic compounds responsible for the coloration in many plants, flowers, and fruits. These compounds are also highly valued for their pharmacological properties. Different anthocyanins such as cyanidin pentoside, cyanidin-3-*O*-glucoside and cyanidin-*O*-hexoside were found by chromatographic examination of *Rubus fruticosus* (Vega et al., 2021). By using chromatografhic techniques, the anthocyanin profile in methanol extracts from the fruits of hybrids (*R. idaeus* / *R. occidentalis*) and five cultivars *of R. occidentalis* was determined. Research findings indicated that *Rubus* spp. (Shuofeng) has a high anthocyanin content and identified cyanidin and pelargonidin as the primary anthocyanin components in this plant (Zhao et al., 2023). In a study using edible berries including *R. fruticosus*, *R. palmatus*, *Rubus* x *medius*, *R. trifidus*, *R. hirsutus*, *R. idaeus*, *R. microphyllus*, anthocyanin contents of berries were analyzed by using quantitative NMR spectroscopy. Among these berries, *R. hirsutus* had the highest total anthocyanin concentration, according to an NMR spectroscopy examination. The two main anthocyanins found are cyanidin-3-glucoside and pelargonidin-3-glucoside (Kumazawa et al., 2024). The anthocyanin content in *Rubus coreanus* known as Korean black raspberries was measured quantitatively through liquid chromatography.

According to the research findings, cyanidin-3-*O*-rutinoside, phelagonidin-3-*O*-glucoside and cyanidin-3-*O*-glucoside are the primary anthocyanins present in *R. coreanus* (Kim et al., 2024). The Chinese raspberry, or *Rubus chingii*, is a plant that grows widely throughout Asia, including China, Japan and Korea. The primary anthocyanins in *R. chingii* consist mainly of cyanidins, including glucosides, sophorosides, rutinosides, sambubiosides, and glucosylrutinosides (Hua et al., 2023). Cyanidin-3-rutinoside and cyanidin-3-glucoside are the two main anthocyanins found in *Rubus discolor*, also known as wild blackberry, according to an examination of its anthocyanin content (Kopjar et al., 2024).

1.2. Tannins

Tannins are widely dispersed, naturally occurring phenolic chemicals that have an astringent quality. They are commonly found in various plant parts and are primarily categorized into hydrolysable tannins, which break down in water, and condensed tannins which are generally more resistant to hydrolysis (Pizzi, 2021). Bolatkyzy's research showed that the major tannin compound in *Rubus vulgaris* is tannic acid (Bolatkyzy et al., 2024). The analysis of tannin content *of Rubus adenotrichos* was indicated that the major tannin compound in the plant is composed of ellagic acid (Schmidt-Durán et al., 2023). A chemical examination of the unripe fruits of *R. chingii* revealed the presence of four ellagitannins: pedunculagin, casuariin, casuarinin, and casuarictin (Li et al., 2019). Phytochemical analysis of leaves of *Rubus chamaemorus* was showed that 4-*O*-α-L-arabinofuranosylellagic acid and epicatechin (one of the components of the tannin) are the tannins isolated (Whaley et al., 2021). The primary constituents of the tannin content of *Rubus ellipticus*, also referred to as the yellow Himalayan raspberry, were determined to be ellagitannins, specifically lambertianin C and sanguiin H6 (Burlando et al., 2023). The presence of many tannin compounds was discovered by the phytochemical investigation of *Rubus ulmifolius*. The hydromethanolic extract of *R. ulmifolius* fruits sourced from Italy includes chlorogenic acid (one of the components of the tannin). On the other hand, the ethanolic extract of *R. ulmifolius* fruits collected from the same region contains hydrolyzable tannins, including compounds like pedunculagin and geranin (Candela et al., 2021).

1.3. Terpenoids

Terpenoids are found in large quantities in the kingdom of plants and have a number of uses. Phytochemical analysis of leaves of *R. suavissimus* and *R. chingii* Hu was indicated that rubusoside which is diterpenoid glycoside found in the plants. Rubusoside is used as bioactive sweetener (He et al., 2023; Liu et al., 2024). One of *R. chingii*'s distinctive diterpenes is goshonoside. While goshonoside G is found solely in fruits, goshonoside F1, F2, F3, F4, and F5 are only found in leaves (He et al., 2023; Z. Liu et al., 2023). A study using a steam distillation extract of *R. idaeus* leaves revealed that the sesquiterpene β-caryophyllene and β-linalool, geraniol, 1,8-cineole and α-citral found terpenoids in the plant (De Santis et al., 2022). Linalool, α-terpineol, and geraniol are the main monoterpenes found in *Rubus rosifolius* essential oil profiles, whereas δ-cadinene has been determined as a sesquiterpene (Rambaran & Ginigini, 2020). In a research on anti-*toxoplasma* activity and chemical compositions of aquatic extract of *Rubus idaeus* L., m-cymene and carvone were identified as monoterpenes whereas anethole has been identified as sesquiterpenes (Mohammad Rahimi et al., 2020).

1.4. Phenolic acids and flavonoids

The plant tissues of *Rubus* species are abundant in phenolic compounds, which contain an aromatic structure with one or more hydroxyl groups that can be free or substituted. A study analyzing *R. fruticosus* L.'s cultivars indicated that kaempferol-3-*O*-glucoside, myricetin, ellagic acid, catechin, chlorogenic acid, *p*-coumaric acid, quercetin-3-*O*-rutinoside, kaempferol, quercetin-3-*O*-glucoside, and hydroxybenzoic acids detected in these cultivars (Čechovičienė et al., 2024). HPLC analysis of *R. ellipticus* indicated that kaempferol was one of the main compounds was identified (Muniyandi et al., 2019). Studies on the aerial parts of *Rubus niveus* indicated that gallic acid, quercetin and rutin are major compounds were detected (Pancholi & Rana, 2020). In a study of chemical composition of *Rubus ulmifolius* Schott indicated that gallic acid was the major phenolic acid identified. Also, the flavonoids with the highest quantities were quercetin and isoquercitrin (Schulz et al., 2019). Analysis of chemical composition identification of *Rubus glaucus* Benth examined that β-sitosterol and campesterol are the phytosterols existing in the extract prepared from fruits of *R. glaucus* Benth (Álvarez & Hurtado, 2024). Study analyzing of chemical composition of *Rubus caesius* indicated that rutin, hyperoside, naringenin 7-*O*-glucoside, tiliroside, astragalin and luteoloside are the flavonoid glycosides identified from the ethanolic extract prepared from *R. caesius* leaves (Hering et al., 2022).

2. Biological activities of *Rubus* species

2.1. Antidiabetic activity

One strategy to control blood glucose levels in diabetic patients is to inhibit enzymes that hydrolyze carbs, such as pancreatic α-amylase, which lowers the gastrointestinal system's absorption of glucose. In a study using the root parts of *R. sanctus*, potential α-amylase inhibitory activity was found in methanol, aqueous, acetone, and hexane fractions; IC_{50} values ranged from 20.12 to 50.9 µg/ml. The α-amylase inhibitor acarbose was used to compare this effect. The most active fraction; methanol, had an IC_{50} value of 20.12 µg/ml, while acarbose had an IC_{50} value of 6.56 µg/ml. These extracts were found to have nearly the same α-amylase inhibitory potential as acarbose (Jaradat et al., 2021a).

Also, with an approximate IC_{50} of 269.94 µg/mL, methanol extract from *R. ellipticus* leaves demonstrated a moderate level of α-amylase inhibition. The authors proposed that the antidiabetic properties of this species might result from its antioxidant properties (Subba et al., 2019).

In another study using a polyphenol-enriched extract of the fruits of *R. chingii* Hu claims that *R. chingii* may help mice with streptozotocin (STZ)-induced diabetes by reducing a number of diabetes symptoms including preventing the pancreas from being destroyed by streptozotocin, lowering hyperglycemia, reversing the atrophy of skeletal muscle and weight loss. Mice with STZ-induced diabetes were given aqueous extract of *Rubus chingii* fruits as 30 mg/kg every day for 18 days, and the anti-diabetic effects were evaluated. In comparison to mice given STZ alone, the anti-diabetic effects of *R. chingii* extract (30 mg/kg) given daily for 18 days to STZ-induced diabetic mice were assessed. These study findings imply that *R. chingii* may be an effective treatment for the symptoms of diabetes and hyperglycemia (Huo et al., 2021).

Furthermore, the antidiabetic qualities of fruit extracts from *R. fruticosus* L. at various stages of maturity were studied by Akyüz in 2022. Study findings demonstrated significant inhibitory effects on the enzyme α-amylase, which are essential for postprandial glucose management. Ethanol and water extracts of the immature, intermediate, and ripening phases of *R. fruticosus* L. showed antidiabetic benefits through different levels of α-amylase enzyme inhibition. Strong α-amylase inhibition was shown by water extracts, especially in the intermediate stage. Acarbose, an antidiabetic medication, was also used to compare the extracts' inhibitory properties. Based on fruit ripeness, the results indicate that *R. fruticosus* fruit extracts are effective natural antidiabetic agents that may be used to treat postprandial hyperglycemia (Akyüz, 2022).

Two varieties *Rubus rosifolius* were studied by Rambaran in order to investigate the hypoglycemic effect of fruit extracts made of *n*-hexane, ethyl acetate, and methanol. Fasting blood glucose levels were examined. 50 mg/kg of the extracts were administered orally to each animal, while 15 mg/kg of metformin served as a positive control. Analyses showed that, out of all the extracts, *n*-hexane extract had the strongest hypoglycemic activity. The oxidized triacylglycerol extracted from the *n*-hexane extract shown more activity and was more effective at reducing blood glucose levels than metformin and hypoglycemic medications. The oxidized triacylglycerol had a notable hypoglycemia effect over metformin for the first half hour (Rambaran et al., 2020).

2.2. Hepatoprotective activity

In a study conducted with ethanolic extract prepared from all parts of *R. sanctus* oral administration of 40% ethanol over 21 days followed by a single subcutaneous injection of CCl_4 caused significant hepatocellular damage in rats. A significant rise in the rats' serum enzyme activity (ALT, AST, ALP, and γ-GT) indicated this damage. These increased enzyme levels were decreased after the administration of ethanolic extract orally. The effects of *R. sanctus*'s ethanolic extract were comparable to those seen in the silymarin-treated group (Badr et al., 2009).

In another study done by VandenAkker (2020), the hepatoprotective effect of *R. idaeus* enriched diet on obese rats was observed. Eight weeks of an 8% *R. idaeus*-enriched diet were followed by measurements of plasma triglycerides (TGs), total cholesterol, High density lipoprotein cholesterol (HDL-C), Non-high density lipoprotein cholesterol (non-HDL-C), and hepatic triacylglycerol (TG) concentration. A diet supplemented with *R. idaeus* was found to diminish hepatic TG accumulation in obese rats while decreasing plasma TG, plasma cholesterol and HDL-C (VandenAkker et al., 2021).

2.3. Antimicrobial activity

R. idaeus leaves extracts were tested for antimicrobial activity against two strains of yeast (*Saccharomyces cerevisiae* and *Candida albicans*) and four Gram-negative (*Enterobacter aerogenes, Escherichia coli*, *Salmonella typhimurium* and *Pseudomonas aeruginosa*) as well as four Gram-positive (*Enterococcus faecali*, *Staphylococcus aureus*, *Listeria monocytogenes* and *Bacillus subtilis*) bacteria. Gram-positive bacteria were effectively inhibited

by the extracts, as evidenced by inhibition zones ranging from 9.0 to 21.0 mm. However, they did not demonstrate any antibacterial action against Gram-negative bacteria, with the exception of *S. typhimurium,* which had inhibition zones between 9.0 and 18.3 mm. Notably, *E. coli* and *E. aerogenes* showed resistance to the extracts. Furthermore, there was no biological activity of raspberry plant components against *S. cerevisiae, E. aerogenes*, *E. coli* and *C. albicans* (Ispiryan et al., 2024).

In addition, ethanolic extract from *R. fruticosus* L. fruits was used against both Gram-negative (*E. coli, P. aeruginosa, Vibrio harveyi,* and *Proteus mirabilis*) and Gram-positive (*S. aureus, B. subtilis*, *Enterococcus hirae*, and *Enterococcus faecalis*) bacteria. The antibacterial activity assessment was carried out using a well- diffusion assay. Every extract that was tested shown efficacy against the bacterial species that were examined in this investigation. With inhibition zones measuring 8.53 mm and 9.85 mm, respectively, *S. aureus* and *E. coli* were the Gram-positive and Gram-negative bacteria that reacted most favorably to these treatments (Salah-Eldin et al., 2024).

Furthermore, antibacterial activity against *S. aureus* and *E. coli* was tested in aqueous and methanol extracts of the leaves, flowers, fruit, and stem of *Rubus ellipticus* known as Himalayan yellow Raspberry. The antibacterial activity of plant extracts were evaluated using the agar well diffusion method and the minimum inhibitory concentration (MIC) assay. *R. ellipticus* methanol fruit and leaf extracts demonstrated antibacterial activity against *S. aureus* with 19 mm and 7 mm zones of inhibition, respectively. Effective antibacterial activity against *S. aureus* was demonstrated by *R. ellipticus* methanol leaf and fruit extracts, with MIC values of 0.203 mg/ml and 0.813 mg/ml, respectively (Das et al., 2021).

The antibacterial properties of methanolic and aqueous extracts of leaves and stems as well as juice of *Rubus canescens* DC. were investigated against a range of Gram-positive and Gram-negative bacteria using the disc-diffusion method. Gram-positive bacteria *Streptococcus pneumonia*e and Methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacteria *E. coli* and *Klebsiella pneumoniae*, were the bacterial isolates that were used. *K. pneumoniae* and *S. pneumoniae* were not affected by fruit juice, leaf and stem aqueous and methanolic extracts, or both. Fruit juice was the only substance that reduced *E. coli* growth, with an average inhibition zone of 18 mm. The antibacterial activity of *R. canescens* DC leaf aqueous extract against MRSA was found to have an average inhibition zone of 46 mm (Assafiri et al., 2020).

Ethanol, acetone, methanol, and aqueous extracts of the fruits of *Rubus discolor* were tested for their antibacterial properties against *Micrococcus flavus*, *E. coli, L. monocytogenes, P. aeruginosa,* and *S. typhimurium*. Ampicillin was the positive control for the assay. The minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of the extracts ranged from 1.2 to 5.0 mg/mL, whereas ampicillin showed values between 0.2 and 1.2 mg/mL. Gram-positive bacteria were more susceptible to the effects of all extracts than Gram-negative bacteria. The most susceptible Gram-positive and Gram-negative bacteria, respectively, to the ethanol extracts were *L. monocytogenes* and *S. typhimurium* (Veličković et al., 2021).

2.4. Antioxidant activity

Studies on the antioxidant activity of the Siberian raspberry, *Rubus matsumuranus* H. Lev. & Vaniot, were conducted. A methanol extract of *R. matsumuranus* leaves was prepared for the DPPH scavenging experiment. The scavenging ability of the *R. matsumuranus* methanol extract (1000 µg/mL) against DPPH was investigated using a microplate spectrophotometric test. The microplate spectrophotometric assay demonstrated excellent scavenging action with an IC_{50} value of 24.68 µg/mL (Kashchenko et al., 2021).

In a study conducted with extracts and fractions of *R. caesius* leaves, (water, 50% methanol, ethyl acetate, chloroform /diethyl ether, methanol and *n*-butanol) antioxidant capacity is analyzed by 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assays. Ethyl acetate fraction of *R. caesius* leaves exhibited the strongest antioxidative activity, while the water extract showed the lowest activity (Grochowski et al., 2019). In another study, the ferric reducing power (FRAP), metal chelating assay, and ABTS radical scavenging test were used *in vitro* models to evaluate the antioxidant property of an aqueous extract prepared from the aerial parts of *R. sanctus*. Trolox served as the control in the $ABTS^{\bullet+}$ radical scavenging activity assessment, and *R. sanctus* extract showed ABTS radical scavenging activity of 98.9%, which was comparable to Trolox's (99.9%). Ferrozine creates colored complexes with Fe^{2+} ions. However, the presence of an efficient chelating agent disrupts this complex formation, which lowers the complexes' red color intensity. EDTA was used as positive control (99.7 %). *R. sanctus* has cheating ability at 3 mg/mL with 90.1%. According to ferric reducing power assay (FRAP), reducing capacity of *R. sanctus* at 3 mg/mL was found 2.281 which is higher than ascorbic acid's reducing capacity. Ascorbic asid was used as control the reducing

ability at 3 mg/mL was found 2.199 (Deliorman Orhan & Hoşbaş Coşkun, 2019).

Shoukat et al., focused on the the antioxidant activity of both *R. idaeus* and *R. strigosus* fruits by the help of two methods; free radical cleansing and ferric reducing antioxidant power methods. The antioxidant properties measured by the radical scavenging method and ferric reducing antioxidant power showed similar results. For both species examined, the free radical scavenging percentage in *R. idaeus* ranged from 55.2 mg/mL at the immature stage to 81.4 mg/mL at full maturity. In *R. strigosus*, this percentage ranged from 56.1 mg/mL at the immature stage to 89.2 mg/mL at full maturity. There was a significant difference in antioxidant activity across stages immature, semi-ripe, and fully mature in both species. However, in the mature stage, the free radical scavenging percentage did not significantly differ between the two species (Shoukat et al., 2022).

The antioxidant activity of *R. fruticosus* L. was analyzed by applying DPPH and FRAP assay. Ethanol, acetone, methanol and acetonitrile extracts were prepared. According to both the FRAP and DPPH techniques, the extract prepared with acetonitrile had the maximum antioxidant capacity. The DPPH radical is less effectively bound by components extracted with higher polarity solvents (e.g. ethanol polarity index: 0.654) than by those extracted with lower polarity solvents (e.g. acetonitrile polarity index: 0.460) (Albert et al., 2022).

Furthermore, the antioxidant potential of distilled water extracts from *Rubus apetalus* Poir. and *Rubus steudneri* Schweinf. leaves was investigated in rats with diabetes induced by alloxan. The animals were separated into groups as normal control, diabetic control, tested groups and diabetic animal receiving antidiabetic drug glibenclamide. Animals tested were feeded after intraperitoneally injection of alloxan monohydrate in saline. Animals received oral treatments oral administration of leaf extracts from *R. steudneri* Schweinf. and *R. apetalus* Poir. as 150 mg/kg and 300 mg/kg was administered to the animals. The animals' organs were dissected for study and blood samples were gathered. The livers of both normal and treated animals were examined for levels of glutathione (GSH), malondialdehyde (MDA), superoxide dismutase (SOD), total thiols, and catalase (CAT). *R. apetalus* and *R. steudneri* leaf extracts both enhanced the antioxidant activity with increased SOD, GSH, total thiols, and catalase findings (Hi, 2019).

2.5. Anti-inflammatory activity

A new pectin polysaccharide that was obtained from *R. chingii* Hu was tested for its anti-inflammatory properties in mice with colitis produced by dextran sulfate sodium (DSS). Following the administration of polysaccharides and anti-inflammatory medications, the findings of the DAI score showed that the test group receiving high-dose polysaccharide treatment was able to successfully reduce the symptoms of colitis. Inflammatory factors IL-6 and TNF-α in colon tissue was remarkably elevated. Inflammatory factors IL-6 and TNF-α are much lower in the high dosage polysaccharide treatment group than in the DSS-induced colitis mice group. According to the findings, polysaccharides can reduce intestinal inflammation by preventing inflammatory agents (Kong et al., 2022).

By identifying COX-2 inhibitory activity and anti-hyaluronidase activity, the anti-inflammatory properties of an aqueous extract made from the leaves of the *R. fruticosus* cultivars Chester, Loch Ness, Loch Tay, and Ruczaj were examined. One of pro-inflammatory compounds is hyaluronidases. The anti-hyaluronidase activity of each of the four cultivars of water extracts was assessed. The Ruczaj and Loch Tay varieties had the most activity with IC_{50} values of 129.30 and 127.36 µg/mL, respectively. The percentage of COX-2 inhibition of was similar for all tested variants. The best results are shown by the strongest COX-2 inhibition and the lowest IC_{50} (Paczkowska-Walendowska et al., 2021).

In an investigation carried out with leaves of *Rubus suavissimus* S. Lee, the inhibitory effect of ethanolic extract on H_2O_2-induced inflammation in retinal pigment epithelial cells was anayzed**.** Present study has demonstrated that H_2O_2 administration induces inflammation in ARPE-19 cells. ELISA was used to assess the secretion of TNF-α, IL-1β, and IL-6 in cell culture, showing that these inflammatory markers were significantly elevated in ARPE-19 cells. Treatment with RS extract reversed H_2O_2-induced cytokine expression, leading to a decrease in proinflammatory cytokine production (Liu et al., 2023).

In another study, the impact of reducing inflammation of aqueous extract prepared from fruits of *R. coreanus* on atopic dermatitis which is chronic inflammatory skin disease was examined using HaCaT cells. TNF-α (Tumor Necrosis Factor Alpha), IL-6 (Interleukin 6), and IL-1β (Interleukin 1β) are proinflammatory cytokines that help cause systemic inflammation. Expression levels of all genes were examined using real-time PCR. In TNF-α/IFN-γ-stimulated HaCaT cells, the mRNA expression levels of these cytokines markedly elevated. However, treatment of these stimulated cells with RCW led to a dose-dependent reduction in the mRNA expression of TNF-α, IL-6, and IL-1β.

These findings indicate that RCW effectively reduces inflammation (Pyeon et al., 2021).

In a study conducted with ethanolic extacts of mature and immature fruits of *R. occidentalis*, the extracts were used on pain management in an operated rat model. The rats received an intraperitoneal injection of several doses of ethanolic extracts of both mature an immature fruits of *R. occidentalis* two hours following the plantar incision. Rats' blood samples were taken after injection, and tests for TNF-α, IL-1β, and IL-6 were conducted. The study's findings showed that intraperitoneal administration of ethanolic extracts of *R. Occidentalis*'s immature fruits had a dose-dependent analgesic effect in the rat model. At 24 and 48 hours following surgery, ethanol extracts from *R. occidentalis* immature fruits dramatically decreased proinflammatory cytokine levels, and compared to mature *R. occidentalis* fruits, ethanolic extracts of immature fruits showed a greater anti-inflammatory activity (Choi et al., 2023).

2.6. Cytotoxic activity

In a cytotoxicity investigation with aqueous, hexane, methanol and acetone fractions prepared from the root of *R. sanctus*, the cytotoxicity evaluation was conducted on the Hep3B cell line. The impact of these extracts on Hep3B cells' cell cycle stages was investigated. The methanol fraction was identified as the most potent inhibitor due to its ability to extend the G2-M phase over time, thereby reducing the rate of cell proliferation. Furthermore, it was demonstrated that extracts from the roots of *R. sanctus* reduced the secretion of a important marker, α-fetoprotein, by decreasing the cell population in the G1 and S phases while inducing an extended duration of the G2-M phase. Hep3B cells treated with aqueous, methanol, acetone, and hexane fractions showed a drop in average levels of α-fetoprotein (AFP) from 1205 ng/ml to 355, 530.6, 237, and 268 ng/ml, respectively. The greatest notable suppression of α-fetoprotein secretion was observed in the acetone fraction (Jaradat et al., 2021b).

In another study, the MTT test was used to evaluate the cytotoxic effects on the MCF-7 cell line of methanolic extract and hexane, ethyl acetate, and methanol fractions prepared from *Rubus hyrcanus* roots and leaves. Over the course of 48 hours, the MCF-7 cell line was exposed to each sample at different concentrations. The ethyl acetate fractions from roots and leaves had the strongest cytotoxic effects on the MCF-7 cell line, with IC_{50} values of 247 and 227 µg/mL, respectively (Yousefbeyk et al., 2022).

The acetone extract of *Rubus fairholmianus* roots was tested on the human breast cancer cell line MCF-7 for cytotoxicity study. From this extract, two main components were identified: 1-(2-hydroxyphenyl)-4-methylpentan-1-one (C1), 2-[(3-methylbutoxy) carbonyl] benzoic acid (C2) (George & Abrahamse, 2019). MCF-7 cell viability was shown to decrease after treatment with chemicals C1 and C2. The impact of these substances on cell survival was assessed using the trypan blue viability test. Both C1 and C2 produced a dose-dependent reduction in cell viability, with IC_{50} values determined at 4.69 µg/mL for C1 and 8.36 µg/mL for C2. MCF-7 cells treated with a higher concentration of compound C1 showed a significant decrease in cell count, with cell viability of 21.75%, while those treated with a higher concentration of compound C2 showed cell viability of 48.25% (George & Abrahamse, 2019).

The conducted study with the methanolic seed extract of *Rubus idaeus* L., cytotoxic effects of methanol extracts from *R. idaeus* L. seeds on several human cancer cell lines were evaluated (Simonovic et al., 2021). According to the National Cancer Institute guideline, crude extracts with an IC_{50} value below 30 µg/mL are considered active (Mbaveng et al., 2019). At effective concentrations (IC_{50}<30 µg/mL), the methanol extract of *R. idaeus* L seeds was found to inhibit the growth of A-549 lung cancer cells (Simonovic et al., 2021).

The cytotoxic effects of methanol extracts from *R. idaeus* fruits were evaluated on the hormone-dependent ovarian cancer cell line CHO-K1 using the MTS assay. Methanol extracts were prepared using two different extraction techniques: soxhlet and microwave-assisted extraction, with their efficiencies in producing phytochemical extracts being compared. *R. idaeus* extract obtained through the soxhlet method showed cytotoxicity toward CHO-K1 cells at a concentration of 50 µg/mL. However, the extract produced via microwave-assisted extraction did not show cytotoxicity at 1000 µg/mL (Ryan Deweese et al., 2021).

Conclusions

This review has explored the findings related to the chemical composition and biological effects of *Rubus* species. In numerous studies, the bioactive components of *Rubus* species, including ellagitannins, phenolic acids, flavonoids and anthocyanins, have been demonstrated anti-inflammatory, anti-cancer, anti-microbial, and antioxidant properties. These compounds are the main contributors to the biological activities of *Rubus* species. The chemical diversity within *Rubus* species enhances their potential therapeutic effects and supports the pharmacological use of extracts obtained from these plants.

Better understanding of the structural and functional aspects of these bioactive compounds highlights the importance of *Rubus* species in promoting public health and suggests their promise in future drug discovery. Additionally, further researchs on the bioavailability and biotransformation of these compounds is essential to increase their effectiveness and supporting their clinical applications.

Author contributions

Deniz Oylumlu, Ali Şen: Collection and compilation of data, writing of the manuscript. Ali Şen: Review and editing of the manuscript. Deniz Oylumlu, Ali Şen: Correction and analysis of chemical compounds. Deniz Oylumlu, Ali Şen: Designing, supervising and editing of the manuscript. Deniz Oylumlu, Ali Şen: All authors read and approved the final manuscript.

Declaration of interests

The authors declare that there is no conflict of interest.

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A deep dive into the phytochemical composition of *Murraya koenigii* (curry leaf): Active compounds and their therapeutic implications

Murraya koenigii (köri yaprağı) fitokimyasal bileşimi üzerine derinlemesine bir inceleme: Aktif bileşenler ve terapötik etkileri

Pranjal Sachan[1*], Prachi Shrivastava[2], Akansha Kushwaha[2], Kris Jain[2], Laxmi Kant[2]

[1]Sanskriti College of Higher Education and Studies, Kanpur Dehat, India

[2]Anjali College of Pharmacy and Science, Agra, India

ABSTRACT

Murraya koenigii, commonly known as curry leaf, is native to South Asia and is renowned for its flavor and fragrance in a variety of dishes. Herbal medicines have been used for centuries to treat various illnesses due to their affordability and minimal side effects. In traditional ayurvedic medicine, curry leaf plays a major role. This small deciduous shrub has all the makings of a future industrial product, including nutritional and therapeutic qualities. Research indicates that *Murraya koenigii* has antibacterial, antifungal, and antiprotozoal activities, particularly in its leaves, stems, bark, and oil. The plant's essential oil and extracts have antifungal and antibacterial potentials. Curry leaf may exhibit anticancer effects, potentially attributed to their potent antioxidant properties that help reduce oxidative stress, a known factor in cancer progression. The plant has the potential to be nutritious since it contains fatty acids, minerals, vitamins, carbohydrates and proteins. The whole plant is utilised for its stomachic and tonic qualities. The current study aims to evaluate the global categorisation, origin, morphological characteristics, and traditional uses of curry leaf.

Keywords: *Murraya koenigii*, curry leaf, phytochemical composition, bioactive compounds, antioxidant properties, leaves, extracts, phytoconstituents, therapeutic applications

ÖZET

Yaygın şekilde "köri yaprağı" olarak bilinen *Murraya koenigii*, Güney Asya'ya özgü olup, çeşitli yemeklerdeki lezzeti ve kokusuyla ünlüdür. Bitkisel ilaçlar, uygun maliyetleri ve minimal yan etkilerinden ötürü yüzyıllardır çeşitli hastalıkların tedavisinde kullanılmaktadırlar. Geleneksel ayurveda tıbbında köri yaprağı önemli bir rol oynar. Bu küçük yaprak döken çalı, besleyici ve tedavi edici nitelikler de dahil olmak üzere, geleceğin endüstriyel ürününün tüm özelliklerine sahiptir. Araştırmalar, *Murraya koenigii*'nin özellikle yapraklarında, gövdelerinde, kabuğunda ve yağında antibakteriyel, antifungal ve antiprotozoal aktivitelere sahip olduğunu göstermektedir. Bitkinin uçucu yağı ve ekstreleri, antifungal ve antibakteriyel potansiyellere sahiptir. Köri yaprağı, kanser progresyonunda bilinen bir faktör olan oksidatif stresi azaltmaya yardımcı, güçlü antioksidan özelliklerine potansiyel olarak atfedilen antikanser etkileri sergileyebilir. Bitki, yağ asitleri, mineraller, vitaminler, karbonhidratlar ve proteinler içerdiğinden besleyici olma potansiyeline sahiptir. Bitkinin tamamı stomaşik ve tonik özellikleri için kullanılır. Mevcut çalışmanın amacı köri yaprağının küresel kategorizasyonunu, kökenini, morfolojik özelliklerini ve geleneksel kullanımını değerlendirmektir.

Anahtar kelimeler: *Murraya koenigii*, köri yaprağı, fitokimyasal bileşim, biyoaktif bileşenler, antioksidan özellikler, yapraklar, ekstreler, bitkisel bileşenler, terapötik uygulamalar

***Correspondence:**
pranjupsit@gmail.com

ORCID iD:
0009-0004-8844-5940

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Introduction

The plant curry leaf (*Murraya koenigii*) is a member of the Rutaceae family, which consists of 150 genera and 1,600 species. It is found to be native to South Asia particularly India, Sri Lanka and Bangladesh (Bhusal & Thakur, 2021). The use of *Murraya koenigii* has been documented since the 1st and 4th centuries AD. Tamil and Kannada literature describes *Murraya koenigii* as Kari used as a flavoring agent (Jain et al., 2017). It is considered as one of the essential or fundamental ingredients in South Asian cuisine for its fragrance and aroma (Ghimire & Magar, 2018).

Murraya koenigii (curry leaf) is a common spice and condiment widely used in tropical nations, valued for its ability to retain flavor and other characteristic properties even after drying. The principal components responsible for its distinctive flavor and aroma include pinene, sabinene, caryophyllene, cardinol, and cardinene (Visakh et al., 2023). In addition to its culinary applications, the plant has been traditionally used for its tonic and stomachic properties. It is known to contain a diverse range of bioactive phytochemicals, including lutein, β-carotene, phenolics, essential oils, minerals, proteins, and terpenoids, which contribute to its medicinal and nutritional significance (Datta et al., 2023).

The use of herbal medications for the treatment of a wide range of disorders is advocated due to their cost-effectiveness, efficacy, and limited adverse effects. This section outlines the various applications and benefits of curry leaf. These curry leaf plays a significant role in Indian curries due to their distinctive aroma (Figure 1). It can be used medicinally to cure diabetes, prevent cancer, and treat cardiovascular illnesses (Syaifurrisal et al., 2024). The plant leaves are rich in antioxidants, including lutein, β-carotene, and tocopherol. These compounds exhibit antioxidative and anti-lipid peroxidative properties, protecting the leaves from oxidative damage.

The therapeutic potential of *Murraya koenigii* can be attributed to its rich phytochemical composition, including alkaloids, flavonoids, phenolic compounds, terpenoids, and essential oils. These compounds used a wide spectrum of biological activities such as antioxidant, antimicrobial, anti-inflammatory, antidiabetic, hepatoprotective, and anticancer properties. The plant's unique chemical profile makes it a promising candidate for the development of novel therapeutic agents.

Despite the increasing interest in its medicinal applications, a comprehensive understanding of *Murraya koenigii*'s phytochemical composition and its therapeutic implications remains underexplored. This review aims to delve deeper into the active compounds present in *Murraya koenigii* and elucidate their roles in various biological mechanisms. By synthesizing the latest findings, this study seeks to highlight the plant's potential as a natural source for drug development and to bridge existing gaps in the literature.

The exploration of *Murraya koenigii*'s phytochemistry and pharmacology not only emphasizes its traditional medicinal value but also underscores its potential for addressing contemporary health challenges. This review provides a consolidated perspective for researchers and practitioners, offering insights into the therapeutic applications of curry leaves and paving the way for future studies in phytopharmacology.

Figure 1. Morphology of *Murraya koenigii* leaf

Taxonomic status:

Kingdom:	Plantae
Subkingdom:	Tracheobionta
Superdivision:	Spermatophyta
Division:	Magnoliophyta
Class:	Magnoliopsida
Subclass:	Rosidae
Order:	Sapindales
Family:	Rutaceae
Genus:	Murraya J. Koenig ex L.
Species:	*Murraya koenigii* (L.) Spreng.

Murraya koenigii is a small, deciduous, aromatic shrub that reaches a height of approximately 6–9 meters and is cultivated at elevations of 1500 meters above sea level. The main stem is dark green to brown colored bark with several dots on it that can be flaked off lengthways to expose the white wood beneath (Sarswat & Yaday, 2023).

The leaves are bipinnately compound, measuring 15–30 cm in length and consisting of 11–25 leathery, glandular leaflets. The flavour of the leaves is slightly fragrant, somewhat acidic, and bitter (Ajay et al., 2011). The inflorescence consists of 60–90 bisexual, funnel-shaped flowers, which emit a fragrant scent, are stalked, complete, and have a diameter of 1.12 cm when fully open. It has 4-5 sepals and 10 straight stamens (Sharma et al., 2024).

The fruiting period begins in mid-July and concludes at the end of August, while the blooming phase starts in mid-April and continues through mid-May. The crop is self-pollinating (3. 2 3, n.d.). Each berry is black in colour and with a glossy surface, measures 1.4 to 1.6 cm in length and 1 to 1.2 cm in diameter, and contains 0.76% of volatile oil that is yellow. The fruits are found in compact clusters, with three to eighty fruits per cluster (Goyal et al., 2020). Suckers are produced by the woody, widely distributed roots.

Propagation methods and chromosomal characteristics

Although seeds are commonly used for propagation, alternative methods such as air layering and root suckers have also been explored. Providing partial shade during germination has been found to enhance seedling establishment. The curry leaf plant has a chromosomal number of 18, confirming its diploid nature (Goel et al., 2020).

Extraction of bioactive compounds

Three bioactive carbazole alkaloids mahanine, mahanimbine, and marrayanol have been successfully extracted from fresh curry leaves using acetone, highlighting their potential pharmacological significance (Dwivedi et al., 2024).

This review is crucial to provide a comprehensive understanding of *Murraya koenigii* (curry leaf), focusing on its phytochemical composition and the active compounds responsible for its therapeutic effects. Despite the growing interest in its medicinal applications, a comprehensive understanding of *Murraya koenigii*'s phytochemical composition and its therapeutic implications remain underexplored. By examining the specific compounds found in *M. koenigii*, such as alkaloids, flavonoids, and terpenoids, this study aims to bridge the gap between traditional knowledge and modern pharmacological evidence. A deeper exploration of these compounds will help clarify their role in treating various health conditions and promote the safe, standardized use of this plant in clinical practice.

1. Application of plant

Murraya koenigii (curry leaf) is widely recognized for its culinary, medicinal, and therapeutic applications. Traditionally, it has been an essential ingredient in South Asian cuisine due to its distinctive aroma and flavor, often used in curries to enhance taste, stimulate appetite, and promote digestion (Balakrishnan et al., 2020). Beyond its culinary uses, the plant holds significant medicinal value, having been used in home remedies for centuries.

The leaves possess wound-healing properties and are locally applied to treat external injuries, burns, and venomous bites. In traditional medicine, they are also used for managing rheumatism. When baked or crisped, curry leaves have been reported to help prevent vomiting (Malode et al., 2021). Additionally, grinding the leaves into a fine powder and mixing them with buttermilk is a well-known remedy for stomach discomfort and acts as a natural laxative when consumed on an empty stomach (Figure 2).

Curry leaf juice, when combined with lime and sugar, serves as a treatment for morning sickness, while the consumption of root juice is believed to relieve renal pain. The stem is traditionally used as a natural teeth-cleansing agent, contributing to gum strength (Chauhan et al., 2017). Furthermore, the plant exhibits anti-astringency properties, and its juice has been used in the treatment of kidney pain (Raghavan, 1957).

Nutritionally, curry leaves are beneficial in addressing calcium and vitamin deficiencies, as well as anemia. The plant has also demonstrated antitumor, hypoglycemic, and anti-hypercholesterolemic properties. Additionally, it has been reported to exhibit anti-inflammatory, antipruritic, and antipyretic effects, making it useful for reducing body temperature (Choo et al., 2020).

In Ayurveda, curry leaves are traditionally used to manage hysteria, rheumatism, hepatitis, cough, and hypertension. A well-known Ayurvedic preparation involves cooking curry leaves with coconut oil until a residue forms, which is then used as a hair tonic to maintain natural hair color and stimulate hair growth (Kundu et al., 2020).

The diverse medicinal and therapeutic applications of *Murraya koenigii* highlight its importance in traditional and modern healthcare practices, warranting further scientific exploration for its pharmacological potential.

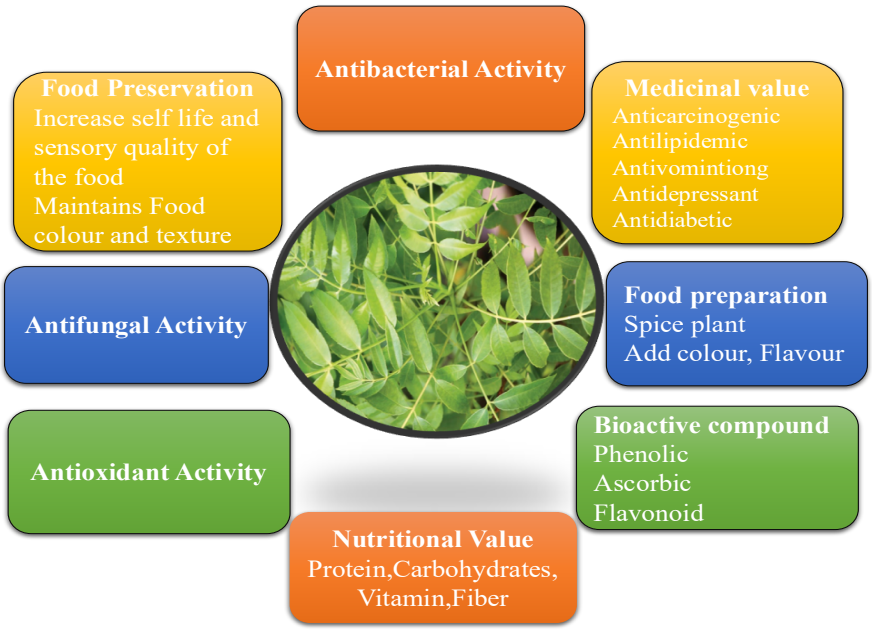


Figure 2. Demonstrating the diverse applications of *Murraya koenigii* (curry leaf)

2. Medicinal uses of *Murraya koenigii*

The plant contains a variety of essential oils, including α-pinene (39.93%), sabinene (13.3%), and trans caryophyllene (9.02%), and has been shown to have antibacterial properties against *Proteus vulgaris*, *Bacillus subtilis*, and *Corynebacterium pyogenes* (Gahtori et al., 2022).

The carbazole alkaloids are found in leaves, fruits, roots and bark of the plant having antidiabetic, anticancer, antibacterial and anti-oxidant properties. The n-hexane seeds extract produces three bioactive carbazole alkaloids namely kurryam (I), koenimbine (II) and koenine (III) and it has been shown that compounds I and II suppress the pooling of rats' enter caused by PGE2 and the diarrhoea caused by castor oil (Vidhya et al., 2020).

Three bioactive carbazole alkaloids mahanine, mahanimbine, and marrayanol have been extracted from fresh leaves using acetone. These compounds exhibit significant antibacterial activity as well as inhibitory effects on topoisomerase I and II (Verma et al., 2022).

Additionally, administration of mahanimbine has been demonstrated to result in a reduction in blood sugar levels in Swiss mice. Extracts of curry leaf have also been shown to reduce the number of cancer cells in mice (Bhandari 2022).

The aqueous extracts of the curry plant have been demonstrated to accelerate the healing of wounds. Alcoholic extracts, specifically the ethanol:water (1:1, v/v) extract of *Murraya koenigii* stem bark, along with the crude root extract of the plant, have been shown to exhibit significant anti-inflammatory properties. Aqueous extracts include tannins and carbazole alkaloids that have hepatoprotective effect. The extract of *Murraya koenigii* alcohol:water (1:1) has been shown to have the best free radical scavenging activities and antioxidant properties (Ghasemzadeh et al., 2014).

2.1. Anti-diabetic property of *Murraya koenigii*

In an animal model, the efficacy of curry leaf in regulating blood sugar levels was investigated. "A noticeable decrease in blood sugar levels was observed". The leaf extract has been reported to lower blood sugar levels (Saini & Reddy, 2015).

This function may be comparable to insulin's effect, which decreases blood sugar levels by either raising the synthesis of insulin by the pancreas or increasing the absorption of glucose by cells due to certain enzymes. This suggests that curry leaf might play a role in managing diabetes.

Evidence-based molecular mechanism

Murraya koenigii exhibits a diverse range of biological activities through its influence on various molecular mechanisms, making it a valuable plant in therapeutic research. The antioxidant activity of *Murraya koenigii* is one of its most notable properties, primarily attributed to its rich content of phenolics and flavonoids, which enhance endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase,

thereby mitigating oxidative stress and preventing cellular damage. Additionally, its anti-inflammatory effects are mediated by compounds like mahanimbine, which suppress pro-inflammatory cytokines such as TNF-α and IL-6 through the inhibition of NF-κB signaling (Dwivedi et al., 2024).

The plant also demonstrates significant anticancer activity, with alkaloids such as girinimbine inducing apoptosis in cancer cells via mitochondrial pathways and modulating PI3K/AKT/mTOR signaling to inhibit tumor progression. Furthermore, *Murraya koenigii* exerts neuroprotective effects by reducing oxidative stress in neuronal cells and enhancing acetylcholinesterase activity, offering potential benefits for neurodegenerative conditions like Alzheimer's disease.

Its antimicrobial properties are attributed to its essential oils, which disrupt microbial cell membranes, providing broad-spectrum activity against bacteria and fungi. Moreover, the plant's cardioprotective and hepatoprotective effects are evidenced by its ability to improve lipid profiles, reduce cholesterol, and enhance liver regeneration by counteracting lipid peroxidation. These multifaceted mechanisms highlight *Murraya koenigii* as a promising natural resource for addressing a wide range of metabolic, inflammatory, and oxidative disorders (Mandal et al., 2010).

Regulation of glucose homeostasis

The bioactive alkaloid mahanimbine enhances insulin secretion from pancreatic β-cells, improving glucose uptake in peripheral tissues. Extracts of *Murraya koenigii* modulate key enzymes involved in carbohydrate metabolism, such as α-amylase and α-glucosidase, thereby reducing postprandial hyperglycemia.

Activation of insulin signaling pathways

The plant's polyphenols and flavonoids stimulate PI3K/AKT signaling, which enhances glucose transporter (GLUT4) translocation to the cell membrane, facilitating glucose uptake in muscle and adipose tissues. Downregulation of GSK-3β (Glycogen Synthase Kinase-3β) prevents excessive glycogen breakdown, promoting glucose storage in the liver.

Reduction of oxidative stress and inflammation

Phenolics and flavonoids enhance endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, which reduce oxidative damage to pancreatic β-cells. Mahanimbine and girinimbine inhibit the NF-κB pathway, leading to decreased levels of pro-inflammatory cytokines (TNF-α, IL-6), which play a role in insulin resistance (Sachan et al., 2024).

Pancreatic β-cell protection and regeneration

Studies suggest that curry leaf extracts promote β-cell regeneration by reducing lipotoxicity and preventing apoptosis via mitochondrial-dependent pathways. Inhibition of caspase-3 activity reduces β-cell death, thereby preserving insulin secretion capacity.

Lipid metabolism and insulin sensitivity

Curry leaf alkaloids improve lipid profiles by reducing LDL cholesterol and triglycerides while increasing HDL cholesterol, which is crucial for managing insulin resistance in type 2 diabetes. Inhibition of lipid peroxidation in the liver and pancreas further supports metabolic homeostasis.

2.2. Antihyperlipidemic property of *Murraya koenigii*

In animal studies curry leaf significantly reduced the levels of total cholesterol and triglycerides (fat). It has been reported that curry leaf may have a hypolipidemic (lipid-lowering) effect, resulting in a slower breakdown of fat and cholesterol (Dwivedi et al., 2024).

The reduction of cholesterol and low-density lipids (also known as "bad cholesterol") may be facilitated by curry leaf. However, these studies are insufficient to assess the effects of curry leaf on human health. Further study is required to determine the benefit of curry leaf in regulating cholesterol levels in the human body. Consequently, it is advisable to consult a physician before using curry leaf for cholesterol management (Debosree et al., 2012).

Evidence-based molecular mechanism

The antihyperlipidemic property of *Murraya koenigii* is well-documented, with evidence highlighting its ability to regulate lipid metabolism and improve lipid profiles. Key bioactive compounds such as mahanimbine, carbazole alkaloids, and flavonoids contribute to its lipid-lowering effects by modulating molecular pathways. One primary mechanism involves the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in cholesterol biosynthesis, which reduces plasma cholesterol levels. Additionally, *Murraya koenigii* enhances the activity of lipoprotein lipase, facilitating the hydrolysis of triglycerides into free fatty acids for energy utilization, thereby lowering triglyceride levels.

Studies have shown that *Murraya koenigii* improves the high-density lipoprotein (HDL) to low-density lipoprotein (LDL) ratio by increasing HDL levels while reducing LDL and very-low-density lipoprotein (VLDL) concentrations. Its antioxidant properties also play a critical role in mitigating lipid peroxidation, preventing oxidative damage to lipids, and reducing atherogenic risk. Animal models fed with a

high-fat diet supplemented with *Murraya koenigii* extract demonstrated significant reductions in total cholesterol, triglycerides, and LDL cholesterol, along with improved liver function and reduced lipid accumulation in hepatic tissues.

These findings suggest that *Murraya koenigii* exerts its antihyperlipidemic effects through a combination of enzymatic regulation, antioxidant activity, and advanced lipid transport, making it a promising natural remedy for managing hyperlipidemia and associated cardiovascular risks (Debosree et al., 2012).

2.3. Potential uses of *Murraya koenigii* for skin

One potential benefit of curry leaf and its essential oils is that they may have anti-inflammatory properties. When applied to external, superficial wounds including skin eruptions, burns, and bruises, they have been shown to promote wound healing (Darvekar et al., 2011).

Formulations and lotions containing the essential oils of the leaves may be used for skin whitening, brightening, and moisturizing dry or rough skin. Curry leaf oil may also be helpful in treating skin issues including ringworm, athlete's foot, boils, acne, and pimples (Ningappa et al., 2008).

To find out how curry leaf can help maintain skin health, further study is needed. Thus, people who experience dermatological issues should consult a doctor before using any herbal medications made from curry leave.

Evidence-based molecular mechanism

Murraya koenigii holds significant potential in skincare due to its rich phytochemical composition and diverse therapeutic properties. The plant's leaves are a source of bioactive compounds such as alkaloids, flavonoids, phenolics, and essential oils, which contribute to its antioxidant, anti-inflammatory, antimicrobial, and wound-healing activities. These properties make *Murraya koenigii* an excellent candidate for addressing various skin conditions and promoting overall skin health.

The antioxidant properties of *Murraya koenigii* protect the skin from oxidative stress caused by environmental factors such as UV radiation and pollution, reducing premature aging, hyperpigmentation, and wrinkle formation. Its anti-inflammatory effects, mediated by bioactive compounds like mahanimbine, help alleviate skin inflammation and irritation, making it useful for conditions like eczema, psoriasis, and acne. Furthermore, the antimicrobial activity of *Murraya koenigii*'s essential oils inhibits the growth of bacteria and fungi, effectively preventing and treating skin infections, including acne caused by *Propionibacterium acnes*.

Studies have also highlighted the plant's wound-healing properties, where its flavonoids and alkaloids promote collagen synthesis, enhance fibroblast proliferation, and accelerate tissue regeneration. Topical formulations containing *Murraya koenigii* extracts have shown promising results in improving skin hydration, elasticity, and overall appearance. Additionally, the plant's ability to reduce melanin production offers potential applications in skin-whitening and anti-pigmentation treatments (Darvekar et al., 2011).

2.4. Anti-cancer property of *Murraya koenigii*

Girinimbine, a carbazole alkaloid derived from the roots of *Murraya koenigii*, has been observed to stimulate dose-dependent apoptosis in A549 cells, leading to cell death. Moreover, the author speculates that the conventional mitochondrial pathway, which involves the release of cytochrome C and caspase-dependent apoptosis, may be responsible for the girinimbine-induced cell death (Gahlawat et al., 2014).

Furthermore, it was shown that the carbazole alkaloid in the stem has an effect on the growth of the HL-6024 human leukemia cell line and that the koenoline in the root bark exhibits anticancer activities against KB cell culture (Manandhar, 2021).

Hepatoprotective potential of Murraya koenigii

Curry leaf extract was observed to significantly increase the activity of the liver enzyme that plays a role in the oxidation of lipids in the liver. The study also showed that the extract exhibited hepatoprotective properties, which reduced liver damage (Iyer & Devi, 2008).

Evidence-based molecular mechanism

Murraya koenigii exhibits significant anti-cancer potential, attributed to its diverse bioactive compounds, including carbazole alkaloids (e.g., mahanimbine, girinimbine), flavonoids, phenolics, and essential oils. These compounds exert their effects through multiple molecular mechanisms, making the plant a promising candidate for cancer prevention and therapy.

One of the key anti-cancer mechanisms of *Murraya koenigii* is the induction of apoptosis in cancer cells via mitochondrial pathways. Carbazole alkaloids like girinimbine promote the release of cytochrome c from mitochondria, activating caspase cascades that lead to programmed cell death. Additionally, the plant modulates cell proliferation by inhibiting the PI3K/AKT/mTOR signaling pathway, which plays a crucial role in tumor growth and survival (Sachan et al., 2025).

The anti-inflammatory properties of *Murraya koenigii* further enhance its anti-cancer efficacy. By suppressing the nuclear factor kappa B (NF-κB) signaling pathway and reducing the expression of pro-inflammatory cytokines, it helps mitigate chronic inflammation a major contributor to cancer progression. Its antioxidant activity also plays a vital role in neutralizing reactive oxygen species (ROS), which are implicated in DNA damage and carcinogenesis.

Studies on various cancer cell lines, including breast, colon, liver, and lung cancers, have demonstrated the cytotoxic effects of *Murraya koenigii* extracts. These studies highlight its ability to inhibit cell migration, reduce angiogenesis, and suppress metastasis. Furthermore, the plant has shown synergy with conventional chemotherapy agents, enhancing their efficacy while reducing side effects (Gahlawat et al., 2014).

2.5. Industrial uses of *Murraya koenigii*

Essential oils derived from plants can be added to erythema and sun protection lotions. Several industrial products of the curry leaf plant are made with a volatile oil, crystalline glycoside, and murragin derived from the blossoms (Pharmacognosy of Ayurvedic Drugs, 1957). It may also be utilised for aromatherapy in the soap and cosmetic business (Xie et al., 2006).

Curry leaf include beta carotene, folic acid, riboflavin, calcium, and zinc, these compounds are beneficial to dental health and can be used to make mouthwashes. Curry leaf oil, which is translucent, clear, and yellow, is commonly exported from India. The extract derived from the seeds of the plant can be utilized in the preparation of in skin lightening and rough skin improving creams. *Murraya koenigii* (curry leaf) is increasingly utilized in skin-lightening formulations due to its rich content of flavonoids, phenolics, and vitamin C, which help reduce hyperpigmentation and promote an even skin tone. Its antioxidant properties protect against oxidative stress, while bioactive alkaloids like mahanimbine aid in regulating melanin synthesis. Extracts from the leaves are incorporated into face creams, serums, and herbal masks to brighten the skin naturally. Additionally, curry leaf essential oil is blended with other botanicals for enhanced skin-rejuvenating effects, making it a valuable ingredient in the cosmetic industry. Petroleum ether and acetone extracts from the leaves can be used to prepare larvicide against (Handral et al., 2012).

Food industry

1. Flavoring agent: The leaves are widely used in the food industry as a natural flavor enhancer in spice blends, ready-to-eat meals, and processed foods.

2. Essential oil extraction: Curry leaf essential oil, rich in bioactive compounds such as α-pinene, β-pinene, and caryophyllene, is used for food preservation and flavoring.

3. Nutraceuticals: Extracts from the leaves and seeds are incorporated into functional foods and dietary supplements due to their antioxidant and anti-diabetic properties.

Pharmaceutical industry

1. Drug development: Bioactive alkaloids like mahanimbine and girinimbine present in *Murraya koenigii* exhibit anti-inflammatory, anti-diabetic, and anti-cancer properties, making them valuable for pharmaceutical formulations.

2. Ayurvedic and herbal medicines: The plant is a key ingredient in herbal formulations for treating digestive disorders, diabetes, and neurological conditions.

3. Antimicrobial agents: Extracts are used in developing antimicrobial coatings and natural preservatives in pharmaceutical products.

Cosmetic and personal care industry

1. Hair care products: Due to its rich antioxidant and antimicrobial properties, curry leaf extracts are incorporated into shampoos, hair oils, and hair growth serums.

2. Skincare: The antibacterial and anti-aging properties of curry leaf extracts make them useful in face creams, anti-acne treatments, and natural skin toners.

3. Aromatherapy: Curry leaf essential oil is used in aromatherapy products due to its calming and stress-relieving effects.

Agriculture and pesticide industry

1. Biopesticides: The plant contains natural insecticidal compounds that can be used to develop eco-friendly pesticides.

2. Animal feed supplement: The high protein and mineral content in dried curry leaves make them a potential ingredient in animal feed to enhance nutrition.

3. Soil enhancer: Decomposed curry leaves enrich the soil with organic matter, improving soil fertility.

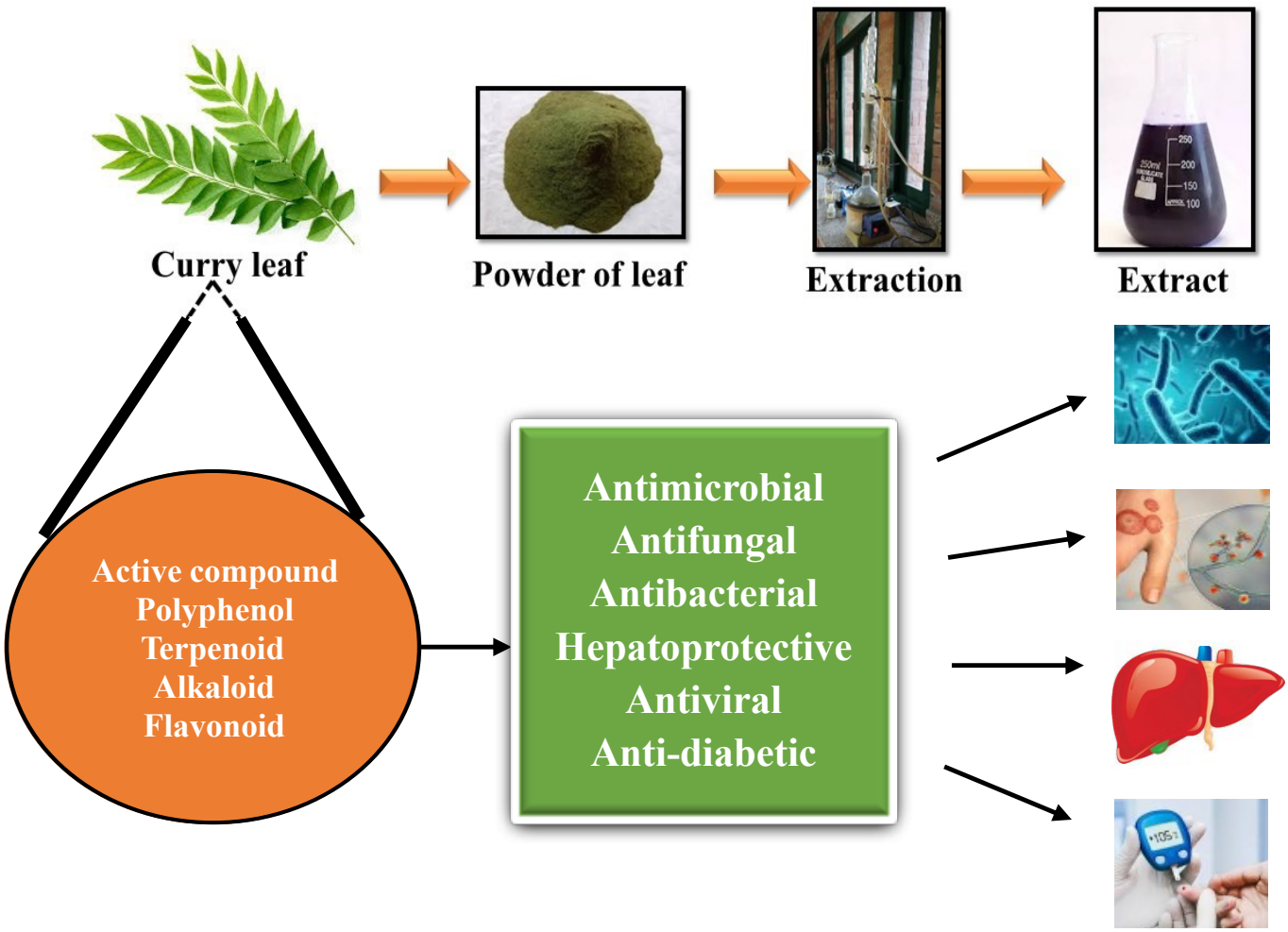


Figure 3. Extraction workflow of *Murraya koenigii* (curry leaf)

Perfumery and fragrance industry

Essential oils: Curry leaf essential oil is used in the production of perfumes, deodorants, and incense sticks due to its unique aroma.

Textile and dye industry

Natural dye source: Extracts from the leaves and bark contain tannins and flavonoids, which can be used for natural fabric dyeing.

Biotechnology and research applications

1. Nanotechnology: Curry leaf extract has been explored for green synthesis of nanoparticles, particularly silver and gold nanoparticles, used in medicine and material sciences.

2. Bioactive compound isolation: The plant serves as a rich source of alkaloids, flavonoids, and phenolics for biochemical research and drug discovery (Dwivedi et al., 2025).

3. Extraction techniques and phytochemical characterization of *Murraya koenigii*

In India and other tropical nations, *Murraya koenigii* (Rutaceae), also known as “curry leaf” in Hindi, is a commonly used as condiment and spice. Extraction of phytochemicals from the plant has yielded a variety of compounds, including acridine alkaloid, bioactive coumarins, and carbazole alkaloid, which are particularly abundant in the leaves. Additionally, phytochemicals such as koenimbin, iso-mahanimbin, and girinimbine have been identified (Chowdhury et al., 2008) (Figure 3).

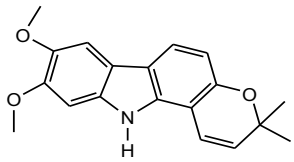
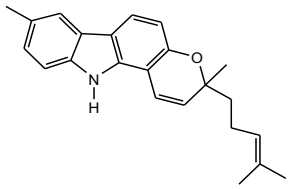
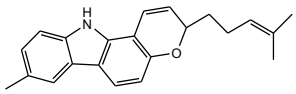
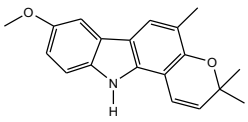
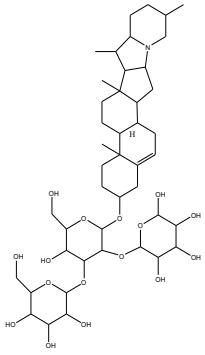
Besides, cyclomahanimbin, tetrahydromahanmbine, murrayastine, and murrayalin have reportedly been found in the leaves. Numerous phytochemicals in *M. koenigii* (curry leaf) are associated with a range of beneficial properties, including anti-diabetic, stimulant, anti-dysentery (Yankuzo et al., 2011), antioxidant, lipid-lowering (Manna et al., 2008), anti-nociceptive, anti-aging, anti-cancer, hepatoprotective, antifungal, and antibacterial activities (Jachak et al., 2024).

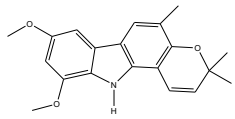
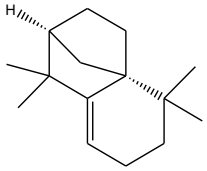
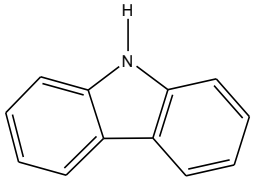
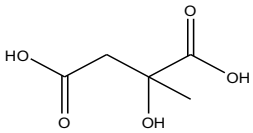
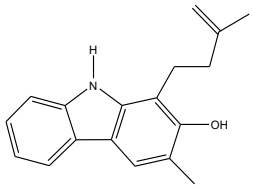
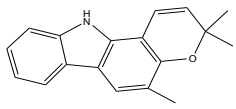
4. Chemical constituents of curry leaf

4.1. Alkaloids

Alkaloids are organic compounds that include one or more nitrogen atoms in a heterocyclic ring. Defining them is challenging because, from a chemical, biochemical, or physiological perspectives, they do not consist of a consistent arrangement of substances (Table 1). There may not be a single, universal definition for alkaloids, despite the fact that they are all nitrogen-containing substances (Singh et al., 2023).

Table 1. Structural representation of alkaloid phytoconstituents in *Murraya koenigii*

Chemical constituents	Plant parts	Pharmacological activities	Mechanisms	Structures	References
Koenigicine	Leaves	Neuroprotective	Decreasing glycemic level		(El-Shiekh et al., 2024)
Mahanimbicine	Leaves	Antiamnesic	Protect against the neurodegenerative diseases		(Guo et al., 2022)
Isomahanimbine	Leaves and roots	Anti-analgesic	Anti-nociceptive effects		(Zou et al., 2023)
Koenimbine	Leaves and roots	Antidiabetic, antiamnesic	Decreases oxidative stress by acting on paraoxonase 1 activity or protect against the neurodegenerative diseases		(Kureel et al., 2017)
Solanine	Leaves, seeds, and fruits	Cytotoxicity, effect on dental caries antioxidant, antimicrobial, antidiabetic, and hyperlipidemic	Inhibition of cavity formation or oxidative stress inducer		(Lawal et al., 2008)

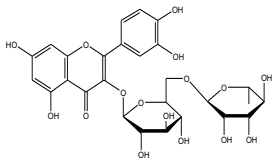
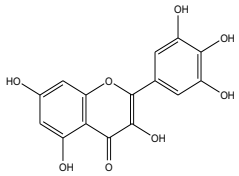
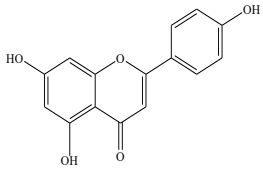
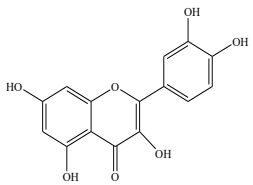
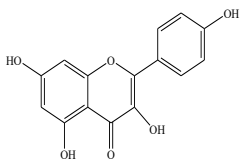
Mukonicine	Leaves	Antioxidant	Increases the GSH Content in the liver and reduction in hepatic malondialdehyde in kidney		(Samanta et al., 2018)
Isolongifolene	Leaves	Antioxidant, neuroprotective	Increases the GSH content in the liver and reduction in hepatic malondialdehyde in kidney or decreasing glycemic levels		(Singh et al., 2014)
Carbazole	Stems		Liver and reduction in hepatic malondialdehyde in kidney		(Rao et al., 2011)
Malic Acid	Stem bark	Antioxidant	Increases the GSH content in the liver and reduction in hepatic malondialdehyde in kidney		(Nigam, 2023)
Mukoenine A	Roots and stem bark	Antidiarrheal	Prostaglandin E2-induced enter pooling and reduction in gastrointestinal motility		(Das et al., 2023)
Girinimbine	Roots, stem bark, and seed	Anti-tumour, antitrichomonal	Act against *Trichomonas gallinae*		(Al Harbi et al., 2016)

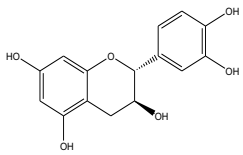
4.2. Flavonoids

Flavonoids are are secondary metabolites that are phenolic and are produced by plants as a defensive mechanism. They are responsible for the production of aromatic compounds and the pigmentation of fruits and plants.

Flavonoids are well recognized for having anti-inflammatory, anti-cancer, and antioxidant properties (Table 2). There are several types of flavonoids, including anthocyanins, flavones, flavanols, and flavanones. In colored rice varieties, anthocyanins are the main flavonoid (Mitra et al., 2012).

Table 2. Comprehensive structural representation and characterization of flavonoids present in *Murraya koenigii*

Chemical constituents	Plant parts	Pharmacological activities	Mechanisms	Structures	References
Rutin	Leaves	Antibacterial, anti-inflammatory	Suppressed activity of proinflammatory cytokines by diminishing TNF-α and IL-1β production in microglia		(Uraku et al., 2015)
Myricetin	Leaves	Anti-cancer, antidiabetic	Reduced production of inflammatory cytokines		(Uraku et al., 2015)
Apigenin	Leaves	Anti-cancer, antioxidant, and anti-inflammatory	Induce muscle relaxation and sedation		(Ningappa et al., 2008).
Quercetin	Leaves	Antibacterial	Promote cell apoptosis		(Ningappa et al., 2008).
Kaempferol	Leaves	Antioxidant, anti-inflammatory	Inhibit signalling pathway		(Ningappa et al., 2008).

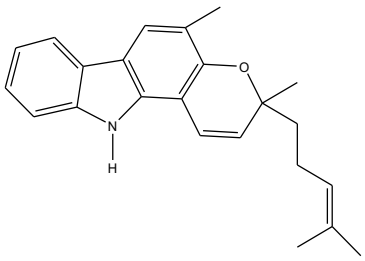
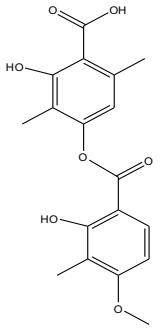
Catechin	Leaves	Vasodilating activity	Inhibit A549 cell by regulating cell cycle arrest		(Uraku et al., 2015)

4.3. Phenolic compounds

Polyphenols consist of phenolic acids, flavonoids, tannins, lignans, and coumarins. Phenols are plant-based antioxidants and the organization of phytochemicals most abundant in entire grains. They exist in various forms, including insoluble, soluble, conjugated, and esterified forms (Sasidharan & Menon, 2011).

The main phenolic acids present in rice are those found in whole grains, namely protocatechuic acid, *p*-coumaric acid, ferulic acid, sinapic acid, and vanillin (Table 3).

Table 3. Structural representation of phenolic compounds in *Murraya koenigii*

Chemical constituents	Plant parts	Pharmacological activities	Structures	References
Mahanimbine	Leaves and bark	Antibacterial, anticancer, apoptotic and anti-invasive potential		(Elumalai et al., 2015)
2-hydroxy-4-methoxy-3,6-dimethylbenzoic acid (Benzoic acid)	Bark			(Joseph & Peter, 1985)

4.4. Terpene compounds

Terpene compounds exist in a wide range of forms and varieties. Their applications are growing in scope as industrial processes continue to progress (Ningappa et al., 2010).

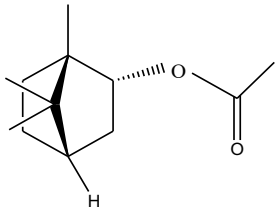
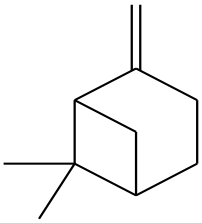
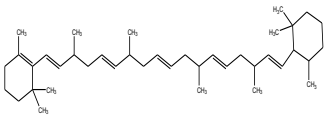
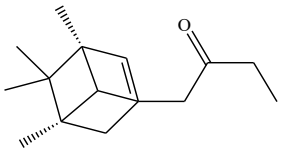
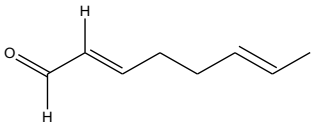
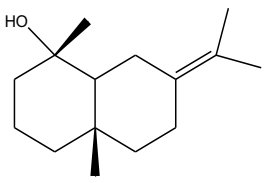
Chinese baijiu is a fermented food and one of the world's six primary distilled liquors. There are several different flavour varieties, the most common of which are twelve (Rastogi et al., 1990).

However, strong flavour varieties, such as those found in Wuliangye and Luzhou Laojiao (sometimes referred to as "Luzhou-flavor liquor") and Maotai and Langjiu (often referred to as "Maotai liquor"), currently dominate the market (Table 4 and Table 5).

Terpenes are primarily used in the pharmaceutical sector as novel anti-cancer medications (Prajapati et al., 2003).

For instance, element, a naturally occurring anti-cancer substance with somewhat harmful side effects, suppresses brain tumours, liver cancer, lung cancer, and nasopharyngeal carcinoma (Rao et al., 2007).

Table 4. Structural representation of terpene phytoconstituents in *Murraya koenigii*

Chemical constituents	Plant parts	Pharmacological activities	Mechanisms	Structures	References
Bornyl Acetate	Leaves, Stems, Roots	Analgesic effect	Inhibits the NF-κB signal pathway		(Khurana et al., 2019)
β-Pinene	Leaves	Antibacterial, antidepressant, cytotoxic, and antimicrobial			(Viswanathan et al., 2020)
Carotene	Leaves	Cancer treatment	Inhibits UV-B carcinogenesis		(Beenakumari et al., 2011)
Chrysanthenyl Acetate	Leaves, Stem	Analgesic effect	Inhibits prostaglandin synthetase		(Khan et al., 1996)
Citral	Leaves, Stems	Antifungal, antibacterial	Inhibited LPS-induced nitric oxide (NO) production		(Igara et al., 2016)
Juniper Camphor	Leaves	Antidiarrheal, anti-inflammatory			(Dasgupta et al., 2003)

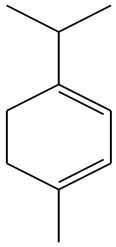
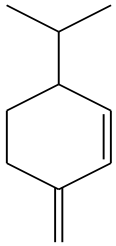
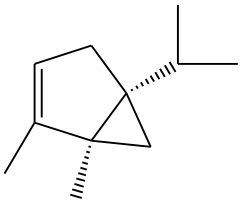
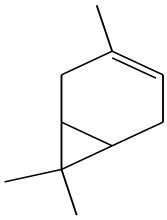
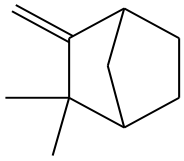
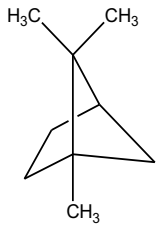
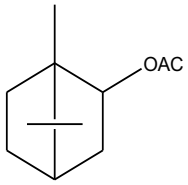
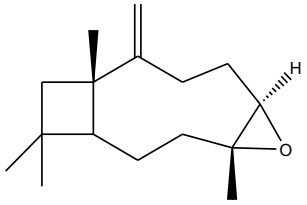
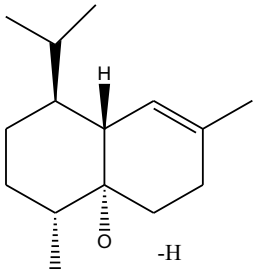
α-Terpinene	Leaves	Antioxidant			(Chelliah et al., 2016)
β-Phellandrene	Leaves	Anti-inflammatory			(Kushwaha et al., 2024)

Table 5. Structural representation of essential oil phytoconstituents in *Murraya koenigii*

Chemical constituents	Plant parts	Pharmacological activities	Structures	References
α-Thujene	Leaves	Anti-ageing		(Rajendran et al., 2014)
3-Carene	Leaves	Antioxidant, antimicrobial		(Raina et al., 2002)
Camphene	Leaves	Anti-cancer		(Rana et al., 2004)

Eucalyptol	Leaves	Anti-cancer		(Wee et al., 2024)
Isobornyl acetate	Leaves	Antimicrobial		(Tripathi et al., 2024)
Beta-caryophyllene oxide	Leaves	Antimicrobial, anti-carcinogenic		(Iqbal et al., 2017)
Cubenol	Leaves	Antioxidant, antimicrobial		(Verma et al., 2023; Chellappandian et al., 2024)

5. Molecular mechanisms and bioactivities of *Murraya koenigii* in therapeutic applications

5.1. Antioxidant

Singlet oxygen (O_2), hydrogen peroxide (H_2O_2), the superoxide anion (O_2•−), and the hydroxyl radical (•OH) are examples of reactive oxygen species (ROS) that are commonly produced as consequences of external stimulation and cellular metabolic activities.

These ROS cause homeostatic abnormalities, which in turn cause oxidative stress, which in turn causes tissue damage and cell death (Nagappan et al., 2011). Biomolecules including lipids, proteins, and nucleic acids can be damaged by ROS at high concentrations (Sharma & Kumar, 2019). Age-related diseases illnesses such as cancer, atherosclerosis, arthritis, and so forth are promoted by unchecked ROS accumulation to grow by unchecked ROS buildup throughout life, even in the presence of antioxidant defense mechanisms such as enzymatic and non-enzymatic antioxidants.

Natural antioxidants derived from plants have been seen as a potentially effective treatment for the avoidance and management of several illnesses, including neurodegenerative (Soundappan et al., 2018).

5.2. Oxidative stress

Free radicals are chemical entities that have one or more unpaired electrons. Reactive oxygen species (ROS) are referred to as "free radicals" in biological systems.

O_2, H_2O_2, and •OH are important ROS (Ramnath er al., 2023). Reactive nitrogen species (RNS), such as peroxynitrite (NO_3^-), NO, and S-nitroso thiols, are known to cause oxidative stress in addition to ROS.

Both ROS and RNS are particularly produced as a component of the cellular defense against invading infections and emerge as intermediates in several metabolic pathways. Additionally, free radicals control a wide range of functions, including as proliferation, glucose metabolism, and cellular growth (El-Shiekh et al., 2024).

5.3. Mitochondrial dysfunction

The main source of high-energy metabolism in cells is the mitochondria, referred to as the powerhouse of the living cell.

Additionally, mitochondria regulate programmed cell death and/or the apoptosis-signaling pathway, scavenge free radicals, and maintain calcium homeostasis (You et al., 2015).

Reduced adenosine triphosphate (ATP) synthesis, elevated reactive oxygen species (ROS) production, compromised calcium buffering, damage to mitochondrial DNA (mtDNA), modified mitochondrial shape, and changes in mitochondrial fission and fusion the consequences of mitochondrial damage include. The ultimate consequence of these processes is cell death.

Presently, the bulk of reactive oxygen species (ROS) are thought to be produced by mitochondrial complexes I and III. This is probably because NADH and dihydroflavine-adenine dinucleotide (FADH2) release electrons into the electron transport chain (ETC) (Hema et al., 2013).

Conclusions

Murraya koenigii (curry leaf) is a valuable plant with diverse bioactive compounds, including alkaloids, flavonoids, phenolics, terpenes, and essential oils. These contribute to its antioxidant, antimicrobial, anti-inflammatory, and antidiabetic properties. Beyond medicinal uses, the plant is applied in culinary, cosmetic, and environmental fields.

Given its value as a natural remedy, curry leaf should be prioritized in the development of new medications. These active compounds have demonstrated potential effects in a variety of health issues, including antioxidant, anti-inflammatory, antibacterial, anti-diabetic, and hepatoprotective properties, making curry leaf a useful plant in both traditional and modern medicine. Its capacity to combat oxidative stress, decrease inflammation, promote metabolic health, and fight infections makes it an important element in natural health formulations.

As research into the particular processes underlying these advantages continues, *Murraya koenigii* may play an even more important role in preventive healthcare and integrative medicine, providing a natural alternative to many synthetic medicines. Further research is anticipated to advance our understanding of its entire therapeutic potential, paving the path for further novel uses in wellness and healthcare. *Murraya koenigii* should be taken into consideration for various clinical and non-clinical research projects in order to thoroughly investigate its pharmacotherapeutics, toxicity, correct standardisation, and clinical trials, all while exploring its many uses.

Because of the potential health benefits of *Murraya koenigii*, future research should also look into its safety to avoid any harmful effects. Understanding its safety, proper use, and how to apply it in treatment is important to make sure it's both effective and safe.

Author contributions

Study conception and design: P.S., A.K., L.K., K.J. Data collection: P.S. and K.J. Analysis and interpretation of results: P.S. and P.S. Drafting of the manuscript: P.S. and P.S. All authors have reviewed the results and approved the final version of the manuscript.

Declaration of interests

The authors declare that there is no conflict of interest.

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Protective effect of microalgae extracts in breast cancer

Mikroalg ekstraktlarının meme kanserinde koruyucu etkisi

Solange Kolie[1], Pınar Altın-Çelik[2], Hamiyet Dönmez-Altuntaş[2], Muazzez Derya-Andeden[2*]

[1]Erciyes University, Institute of Health Sciences, Department of Medical Biology, 38030 Kayseri, Türkiye

[2]Erciyes University, Faculty of Medicine, Department of Medical Biology, 38030 Kayseri, Türkiye

ABSTRACT

Breast cancer is a major global health problem, with an estimated 2.3 million new cases in 2020, making it the most commonly diagnosed cancer in women. Advances in the understanding of genetic and environmental risk factors have contributed to a significant decline in mortality rates over the past three decades and have led to improved diagnosis and treatment strategies. While significant progress has been made in breast cancer awareness and treatment, inequalities in access to care and early diagnosis, particularly in low-resource settings, remain a major challenge. Addressing these gaps is critical to improving outcomes worldwide. Natural treatments for breast cancer are gaining increasing attention as they can complement or enhance conventional treatments while minimizing side effects. Several natural products, including phytochemicals, have shown significant anti-cancer properties through multiple mechanisms, making them promising candidates for the treatment of breast cancer. Microalgae contain several bioactive compounds, including flavonoids and phenolic acids, which have been shown to induce apoptosis and inhibit the proliferation of cancer cells. Microalgae extracts have a significant protective effect against breast cancer through antioxidant activity, apoptosis induction, and immune modulation. Studies show that microalgae such as *Spirulina* and *Haematococcus pluvialis* can inhibit tumor growth and promote cell death in breast cancer models, highlighting their potential as complementary therapies. Although the protective effects of microalgae extracts are promising, to completely comprehend their workings and possible incorporation into traditional cancer treatments, more investigation is required. This review highlights the potential of microalgae and microalgae extracts as a source of anticancer agents based on their efficacy against breast cancer.

Keywords: Microalgae, breast cancer, anticancer, biocompounds, bioactivity

ÖZET

Meme kanseri, 2020 yılında tahmini 2,3 milyon yeni vaka ile kadınlarda en sık teşhis edilen kanser türü haline gelen önemli bir küresel sağlık sorunudur. Genetik ve çevresel risk faktörlerinin anlaşılmasındaki ilerlemeler, son otuz yılda ölüm oranlarında önemli bir düşüşe katkıda bulunmuş ve iyileştirilmiş tanı ve tedavi stratejilerine yol açmıştır. Meme kanseri farkındalığı ve tedavisinde önemli ilerlemeler kaydedilmiş olsa da özellikle düşük kaynaklı ortamlarda bakıma ve erken tanıya erişimdeki eşitsizlikler büyük bir zorluk olmaya devam etmektedir. Bu boşlukları ele almak, dünya çapında sonuçları iyileştirmek için kritik öneme sahiptir. Meme kanseri için doğal tedaviler, yan etkileri en aza indirirken geleneksel tedavileri tamamlayabilmeleri veya geliştirebilmeleri nedeniyle giderek daha fazla ilgi görmektedir. Fitokimyasallar da dahil olmak üzere çeşitli doğal ürünler, birden fazla mekanizma yoluyla önemli kanser karşıtı özellikler göstermiştir ve bu da onları meme kanserinin tedavisi için umut verici adaylar haline getirmektedir. Mikroalgler, apoptozu indüklediği ve kanser hücrelerinin çoğalmasını engellediği gösterilen flavonoidler ve fenolik asitler de dahil olmak üzere çeşitli biyoaktif bileşikler içerir. Mikroalg özleri, antioksidan aktivite, apoptozis indüksiyonu ve bağışıklık modülasyonu yoluyla meme kanserine karşı önemli bir koruyucu etkiye sahiptir. Çalışmalar, *Spirulina* ve *Haematococcus pluvialis* gibi mikroalglerin meme kanseri modellerinde tümör büyümesini engelleyebileceğini ve hücre ölümünü teşvik edebileceğini göstererek, tamamlayıcı terapiler olarak potansiyellerini vurgulamaktadır. Mikroalg özlerinin koruyucu etkileri ümit verici olsa da bunların işleyişini ve geleneksel kanser tedavilerine olası katılımını tam olarak kavramak için daha fazla araştırma gerekmektedir. Bu derleme, meme kanserine karşı etkinliklerine dayanarak, mikroalglerin ve mikroalg özlerinin antikanser ajanları kaynağı olarak potansiyelini vurgulamaktadır.

Anahtar kelimeler: Mikroalgler, meme kanseri, antikanser, biyobileşikler, biyoaktivite

***Correspondence:**
derya.muazzez@gmail.com

ORCID iD:
0000-0003-4390-5769

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Introduction

Cancer covers a wide group of diseases related to the uncontrolled proliferation of cells in the body (Farshi, 2024). There are more than 200 different types of cancer, some of which have the potential to spread to other tissues, often causing fatal metastases. According to data from 2022, approximately 20 million new cases and more than 9.7 million cancer-related deaths occurred worldwide (Liao et al., 2024). Numerous studies have shown that cancer progression is due to activation of tumor formation, DNA damage, abnormal DNA repair mechanisms, inactivation of tumor suppressor activity, metastasis, and increased cell survival through angiogenesis (Niranjana et al., 2015; O'Connor, 2015). Although cancer treatments can be successful in some cancer cases, the applicability of these drugs is limited due to their side effects. Generally, drugs used to treat cancer are highly toxic not only to cancer cells but also to normal cells in the body. Chemotherapy and radiotherapy are some of the current standard therapeutic approaches for cancer treatment. However, there are many side effects of chemotherapy with these chemotherapeutic agents, such as hematopoietic toxicity, anorexia and hair loss, which are usually serious side effects. Therefore, the search for new potential therapeutic agents for cancer treatment is remarkable for the scientific world. Particular focus has recently been placed on some marine substances, including lipids, peptides, carotenoids, and carbohydrates, which have anti-cancer, anti-inflammatory, antimicrobial, and antioxidant properties. Microalgae are very important components of the aquatic ecosystem. Known for their rapid growth cycles, microalgae are increasingly used in the production of food and drugs for human/animal consumption due to their ability to survive in a foreign environment. Prior *in vitro* research has demonstrated that a large number of these bioactive microalgal chemicals exhibit potent anti-human cancers, including breast cancer and leukemia. As a consequence, several mechanisms underlying these bioactive chemicals' anticancer activity have been clarified, including their capacity to target molecular, cellular, and subcellular checkpoints linked to the development and spread of cancer. Recent findings have brought to light a number of the processes by which the bioactive substances generated by microalgae work, including as the inhibition of telomerase and protein kinases and the triggering of autophagy and death. In addition to a decrease in tumor volume, further *in vivo* investigations have demonstrated a potent anti-angiogenesis impact on solid tumors.

These bioactive microalgae compounds have also been studied in the context of clinical trials for various types of cancer, making them strong candidates for the development of antitumor drugs.

Breast cancer

Breast cancer is a heterogeneous disease in which genetic and environmental factors play a role. Breast cancer is a global health problem and the most common cancer in women worldwide (Ferlay et al., 2019; Narayan et al., 2020). Many malignant tumors can metastasize, which means the invasion of cancer cells, and this is the most dangerous feature of cancer (McSherry et al., 2007).

Breast cancer begins primarily in breast cells. Malignant tumors, which are clusters of cancer cells, can spread and damage surrounding tissue and also spread throughout the body. Cancer can cause changes in breast cells that prevent them from growing or functioning normally. These alterations may result in benign tumors like intraductal papillomas or non-cancerous breast conditions like atypical hyperplasia and cysts (Sinha, 2018). However, breast cancer can develop due to modifications in the breast cells. It usually begins in the cells of the ducti, the tubes that carry milk from the mammary glands to the nipple, and is called ductal carcinoma (Edward et al., 2021; Obeagu et al., 2023).

Classification of breast cancer

There are various classification methods for breast cancer in the literature. However, the most commonly used method is the method based on the presence or absence of receptors. Breast cancer is categorized into four groups based on the presence or absence of three receptors for estrogen, progesterone and human epidermal growth factor receptor 2 (HER-2) (Hon et al., 2016). Invasive breast cancer is categorized into four main molecular subtypes using an immunohistochemical technique according to the estrogen receptors expression (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (Joshi & Press, 2018). The luminal A subtype (ER+ and/or PR+ and HER2-) accounts for approximately 60% of breast cancer cases and is associated with a favorable prognosis (Gao & Swain, 2018). The luminal B subtype (ER+ and/or PR+ and HER2+) accounts for 30% of cases and is associated with a high Ki67 index (>14%), a marker of cell proliferation, and a poor prognosis (Ades et al., 2014). HER2-positive breast cancer (ER-, PR- and HER2+) accounts for 10% of cases and is also associated with a poor prognosis (Loibl & Gianni, 2017). Lastly, 15–20% of cases are triple-negative breast cancer/TNBC (ER-, PR-, and HER2-), which is notorious for its high aggressiveness, propensity to strike young women, and exceptionally poor prognosis (Bergin & Loi, 2019). Triple-negative breast cancer (TNBC) is the type with the worst prognosis. It is

characterized by the complete absence of three receptors, which makes it difficult to treat with hormonal and targeted therapies (Podo et al., 2010). These are aggressive tumors, accounting for approximately 12% to 17% of cases, and are characterized by a high nuclear grade, high mitotic activity and significant metastatic potential to internal organs (Foulkes et al., 2010).

Risk factors for breast cancer

Breast cancer is a disease with high risk factors that can be influenced by many factors, including genetic, environmental, behavioral and major lifestyle elements (Mahdavi et al., 2019; Obeagu EI et al., 2021; Ibekwe et al., 2022). Poor lifestyle choices, environmental and socio-psychological factors are all associated with the onset of the disease. Studies have shown that 5-10% of breast cancer cases are due to genetic mutations and family history, while 20-30% are associated with modifiable factors (Sun et al., 2017). Major risk factors for breast cancer include family history, diet, obesity, mutations such as BRCA1 and BRCA2, genetic predisposition, including smoking and alcohol consumption. Other factors such as exposure to ionizing radiation, menstrual cycles, pregnancy and breastfeeding can also play a role in the development of breast cancer (Mahdavi et al., 2019). Other risk factors for breast cancer include older age, female sex, early menstruation, late menopause, nulliparity, non-breastfeeding, dense breast tissue, hormone replacement therapy and a history of breast radiotherapy (O'Sullivan et al., 2018).

Breast cancer treatment

Most cases of breast cancer are detected by mammography or clinical examination (Ruddy & Ganz, 2019), and there are different strategies for its treatment (Barzaman et al., 2020).

Treatment strategies for breast cancer vary depending on the molecular subtype. In addition to locoregional treatments such as surgery and radiotherapy, there are multidisciplinary approaches that also include systemic treatments. These include endocrine therapy for hormone receptor-positive cancers, chemotherapy, anti-HER2 therapy for HER2-positive cancers, bone-stabilizing agents, poly (ADP-ribose) polymerase inhibitors for patients with BRCA mutations, and, more recently, immunotherapy (Harbeck et al., 2019).

Considering the serious side effects, chemical resistance, high cost, and shortage of cancer drugs, scientists have started to look for natural therapeutics to develop new cancer drugs. Natural medicines have minimal side effects and the potential to act on various signaling pathways related to tumor formation. Considering all these advantages, research on natural products is rapidly increasing to search for new anticancer drugs not only from land plants and microorganisms but also from marine organisms (Sung et al., 2021). Future therapeutic approaches aim to personalize treatment and adjust treatment intensity according to tumor biology and initial response to treatment (Harbeck et al., 2019).

Microalgae

Microalgae are a wide range of prokaryotic and eukaryotic microorganisms that are mostly photoautotrophic and occur singly or in colonies. They play an important role on Earth and form the largest biomass on Earth, responsible for at least 32% of global photosynthesis (Priyadarshani et al., 2011). Moreover, these photosynthetic microorganisms have colonized all marine and terrestrial ecological niches and also represent the largest group of living organisms in terms of biodiversity on Earth (Irigoien et al., 2004). Although they are highly biodiverse, they are an almost untapped resource. There are an estimated 200,000 to 800,000 species in many genera, of which only 50,000 are known (Priyadarshani et al., 2011). Because of their high ecological adaptability and constant exposure to a variety of biotic and abiotic stressors, microalgae are a rich source of interesting and useful components (Pulz & Gross, 2004; Spolaore et al., 2006). As photoautotrophic organisms, they are also an effective source of high value-added biomolecules due to their simple growth requirements and short life cycle (Spolaore et al., 2006; Kim et al., 2014; Plaza et al., 2009). Bioactive compounds of microalgal origin can be sourced directly from primary metabolism, such as proteins, fatty acids, vitamins, and pigments, or can be synthesized from secondary metabolism (de Morais et al., 2015). These substances are used in various fields, including medicine, pharmaceuticals, nutraceuticals, cosmetics, energy, etc. Some extensive studies have confirmed the potential of microalgae as a reliable and environmentally friendly raw material for the production of important valuable resources, paving the way for new advances in biotechnology (Bürck et al., 2024). Microalgae such as *Haematococcus pluvialis*, *Dunaliella salina*, *Blakesleatrispora* sp., *Desmodesmus* sp., *Euglena gracilis*, *Tisochrysis lutea*, *Isochrysis galbana*, *Phaeodactylum tricornutum* and *Cylindrotheca closterium* are among the most studied, as they are capable of producing significant amounts of carotenoids (Razz, 2024; Huang et al., 2024). They are microorganisms that synthesize a variety of rare carotenoids and pave the way for innovative industrial and scientific applications. These carotenoids, such as fucoxanthin, xanthophylls and astaxanthin, are

characterized by their high antioxidant and anti-inflammatory properties and contribute to human health and protection against various chronic diseases (Gong et al., 2024).

Microalgae as a source of biocompounds

Nowadays, many industries from various sectors are investing in natural and biologically produced products with high added value (Mahapatra et al., 2018). Pharmaceuticals, cosmetics, food and pet food, polymers, chemicals, and energy products are just a few of the industries that use these products. The use of microalgae is particularly interesting and important due to their cellular composition, which enables the extraction of high-quality commercial products (Kumar et al., 2021; Premaratne et al., 2021). Microalgae synthesize two categories of metabolites, namely primary metabolites and secondary metabolites. Lipids, proteins, and carbohydrates are examples of primary metabolites that are essential to the survival of some microorganisms, whereas carotenoids, astaxanthin, and polyhydroxyalkanoates are examples of secondary metabolites that are functional substances connected to physiological systems (Japar et al., 2021; Liu et al., 2022). They are microorganisms that represent a potential source of raw materials for various bioproducts, mainly due to the primary and secondary metabolites they contain. Lipids can be converted into high-value polyunsaturated fatty acids such as omega-3, while carbohydrates can be potential sources of biohydrogen. Proteins can likely be converted into biopolymers such as bioplastics, and pigments can reach high concentrations of valuable carotenoids (Calijuri et al., 2022). These microorganisms are rich in bioactive components, mainly lipids (7-65%), proteins (5-74%), carbohydrates (8-69%) and to a lesser extent other metabolites such as pigments and vitamins (1-14%), depending on their cell structure (Becker, 2007; Ejike et al., 2017; del Mondo et al., 2020; Siddiki et al., 2022). Proteins, essential amino acids, carbohydrates like glucose and starch, omega-3 and omega-6 fatty acids, and vitamins B1, B2, B5, B6, B9, A, C, and E are all known to be abundant in microalgae (Yan et al., 2016; Chu, 2012). Microalgae extracts (chemical composition) contain carbohydrates, proteins, lipids, vitamins, micronutrients, macronutrients and phytohormones like gibberellins, ethylene, cytokinins, auxins, abscisic acid and other bioactive compounds such as fucoxanthin and phycobiliproteins (Bello et al., 2021). Microalgae biomass is an excellent raw material for the production of biofuels, biomaterials (peptides, proteins, saccharide polymers) and carbohydrates ($Cn(H_2O)n$) for the animal and human food sector (Maurya et al., 2016; Corre et al., 2017). As microorganisms, algae have a lipid composition that generally varies between 20% and 50%, but, based on the strain and culture conditions, can increase to 80%. (Sun et al., 2018). Among the compounds extracted from microalgae, lipids are the most studied and offer significant potential for expansion and commercialization of the process (Maltsev & Maltseva, 2021). Linoleic acid (C18:2 or omega-6) and linolenic acid (C18:3 or omega-3) are among the most popular polyunsaturated fatty acids, mainly because of their benefits and advantages for human health (Sharma et al., 2020), as they can combat numerous diseases such as coronary heart disease, thrombosis, macular degeneration, dementia, diabetes, allergies, asthma, osteoporosis and some cancers. They are currently being investigated as a potential adjuvant treatment for cardiovascular complications associated with COVID-19 as well as many other diseases (Oliver et al., 2020). In addition, long-chain omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (C20:5 or EPA) and docosahexaenoic acid (C22:6 or DHA), are used to feed aquatic organisms in aquaculture (Fernández et al., 2021).

Microalgae are rich sources of phenolic compounds, which are well known for their strong antioxidant and anticancer properties (Cichoński & Chrzanowski, 2022). These bioactive molecules can modulate various cellular pathways, including oxidative stress reduction, apoptosis induction, and inhibition of cancer cell proliferation. Several studies have highlighted the role of microalgal phenolics in suppressing tumor growth through mechanisms such as cell cycle arrest and modulation of key signaling pathways involved in carcinogenesis (Matulja et al., 2022). Moreover, their ability to enhance the efficacy of conventional chemotherapy while minimizing side effects makes them promising candidates for breast cancer treatment. Further research is needed to explore their bioavailability and molecular interactions to fully unlock their therapeutic potential.

Carotenoids are secondary metabolites produced by microalgae. As natural pigments, they are considered healthier than chemically synthesized pigments and are attracting the attention of various industries such as pharmaceuticals, cosmetics, food, and health (Henríquez et al., 2016). The most well-known carotenoids that come from microalgae in the commercial market are β-carotene, lutein, and astaxanthin (Hu et al., 2018; Rammuni et al., 2019). The increasing interest in these substances is due to the antioxidant, anti-inflammatory, vitamin A precursor and neuroprotective properties of microalgae-derived carotenoids (Cezare-Gomes et al., 2019; D'Alessandro & Antoniosi Filho, 2016; Hu et al., 2018). Researchers are currently concentrating on species like *Haematococcus*

pluvialis for astaxanthin (Li et al., 2011; Rammuni et al., 2019), *Murielopsis* sp. and *S. almeriensis* for lutein (Pagels et al., 2020), and *Dunaliella salina* for β-carotene (Pourkarimi et al., 2020; Wu et al., 2020; Xi et al., 2020). Nonetheless, *Chlorella vulgaris*, *Spirulina platensis*, *Haematococcus pluvialis*, and *Dunaliella salina* are the most researched species, according to Silva et al. (2020), who compiled the trends in the brightest pigments and microalgae sources over the previous ten years. Microalgae contain carotenoids such as diatoxanthin, diadinoxanthin, alloxanthin, and peridinin, which are important because they contain a variety of bioactive compounds. These substances have potential uses in several biotechnological fields and are advantageous to human health (Pistelli et al., 2021).

Terpenes are a diverse class of compounds with key ecological roles, including intraspecific communication, chemical defense, and protection against microbial contamination. Although generally classified as secondary metabolites, their isoprenoid precursors also contribute to primary metabolites like chlorophylls, carotenoids, and steroids. Algae, particularly red algae, produce various terpenes such as monoterpenes, sesquiterpenes, and diterpenes, which exhibit antimicrobial, anti-inflammatory, antioxidant, and anticancer properties. These characteristics make terpenes valuable for scientific and industrial applications (Liu et. al., 2024).

Microalgae such as cyanobacteria are indeed an important source of extracellular polysaccharides. They can be used as stabilizers in the food industry and as humectants in cosmetics and pharmaceuticals. Additionally, the human immune system is known to be stimulated by sulfated polysaccharides derived from microalgae (Fu et al., 2019).

Microalgae such as *Spirulina* and *Chlorella vulgaris* are rich in proteins. Studies have shown that the proteins in *Spirulina* can reduce inflammation and allergies, while the peptides in *Chlorella vulgaris* can protect against cell damage. In addition, these microalgae provide essential amino acids that mammals cannot synthesize (Barkia et al., 2019; Lordan et al., 2011).

Using biomolecules extracted from algae as active pharmaceutical ingredients plays a significant role in pharmacy. Most studies on this topic focus on these extracts' total phenolic content and antioxidant activity. Research has been conducted on the *in vitro* antioxidant activities of extracts and/or molecules derived from various *Chlorella* species, their protective effects against radical-induced oxidative stress in kidney cells, and the total phenolic content and antioxidant activity of *Ankistrodesmus* sp. (Ko et al., 2012; Chen et al.,2014; Nakashima et al., 2009; Jerez-Martel et al., 2017).

In a study by Manivannan et al. (2012), the authors assessed *Chlorella marina*'s *in vitro* antioxidant properties to identify safe and inexpensive new antioxidant sources. They prepared algal extracts using methanol, diethyl ether, and hexane solvents and tested their total phenolic content, antioxidant activities, deoxyribose radical scavenging activities, and reducing power. Their results indicated that the methanol extracts of *C. marina* might possess potential antioxidant effects (Manivannan et al., 2012).

Shanab et al. (2012) evaluated the antioxidant and anticancer activities of aqueous extracts from 9 microalgae species, including 8 cyanobacteria and 1 green alga (*Chlorella vulgaris*). The extracts were first evaluated for their total phenolic content, secondary metabolites such as terpenoids and alkaloids, and phycobiliprotein pigments like phycocyanin. Then, the antioxidant activities of the algal extracts were assessed. Finally, the effects of the extracts on the proliferation of HepG2 and EACC cancer cells were evaluated by calculating cell viability percentages. They found that *C. vulgaris* exhibited anticancer activity (Shanab et al., 2012).

Stress responses and tolerance mechanisms in microalgae

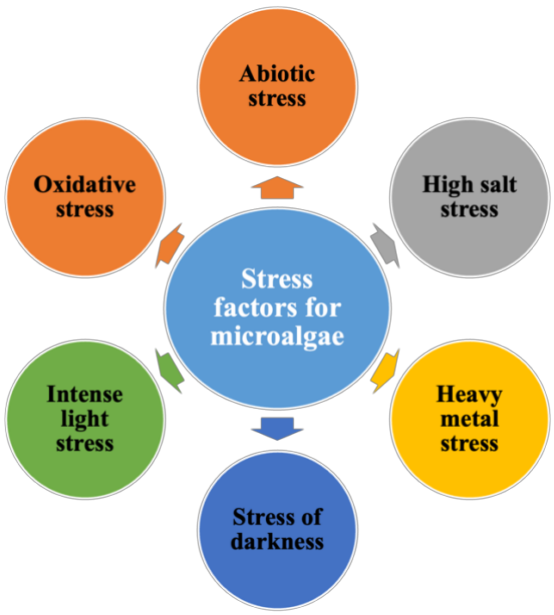

Figure 1. Stress factors for microalgae

Factors such as abiotic stress, high salt stress, oxidative stress, intense light stress, darkening stress and heavy metal stress can cause stress in microalgae (Figure 1). Stress factors can cause changes in the physiological and biochemical processes of microalgae and affect growth, photosynthesis, cellular ultrastructure, protein content and fatty acid composition. These stress factors can also trigger

the production of reactive oxygen species (ROS), which cause the oxidation of proteins, lipids and peptides and stimulate the antioxidant system (Xiao et al., 2023; Singh et al., 2018).

Responses of microalgae to abiotic stress

Microalgae demonstrate high tolerance to abiotic stressors and produce valuable metabolites. Exposure to nutrient deficiency, intense light, extreme temperatures, high salinity, or heavy metals can stimulate lipid and by-product biosynthesis (Paliwal et al., 2017; Chen et al., 2017). Nutrient deficiencies, particularly in nitrogen, phosphorus, and metal ions, are known to enhance lipid accumulation (Chen et al., 2011; Fernandes et al., 2013; Pancha et al., 2014). One well-studied species, *Chlorella protothecoides*, produces significant lutein and fatty acids suitable for biodiesel (Campenni' et al., 2013). While continuous stress promotes lipid or carbohydrate accumulation, balancing it with growth rate is crucial to maintaining productivity and reducing biofuel costs (Pancha et al., 2015).

Under stress, microalgae produce polyunsaturated fatty acids and adapt by modifying their membrane composition and accumulating compatible solutes. Salt stress, for instance, enhances carotenoid synthesis, likely due to increased reactive oxygen species (Li et al., 2009). Salt-tolerant species like *Dunaliella salina* produce osmoprotective solutes such as sucrose, glycerol, and betaine, aiding survival under extreme salinity (El Arroussi et al., 2015).

Responses of microalgae to high salt stress

Microalgae species adapt to extreme salinity through metabolic changes (Gebser & Pohnert, 2013; Paliwal et al., 2017). Elevated salt levels inhibit growth in freshwater algae such as *Chlorella vulgaris*, *Chlorella salina*, *Chlorella emersonii* (Talebi et al., 2013) and *Scenedesmus opoliensis* (Demetriou et al., 2007). In *Chlamydomonas*, high salt stress slows cell division, reduces size, and induces palmelloid formation, a transitional stage where cells lose flagella, secrete exopolysaccharides, and cluster together (Hema et al., 2007; Khona et al., 2016). *Chlorella* and *Dunaliella* respond differently to salt stress. *Chlorella* relies on osmoregulation through organic solutes and inorganic ion accumulation, while *Dunaliella*, lacking a rigid cell wall, rapidly adjusts turgor pressure by modulating intracellular ion and glycerol concentrations (Shetty et al., 2019; Kaçka & Dönmez, 2008).

Responses of microalgae to heavy metal stress

Recent studies have examined heavy metal stress in microalgae such as *Chlorella*, *Scenedesmus*, cyanobacteria, and *Chlamydomonas reinhardtii*, revealing species-dependent toxicological responses (Geng et al., 2022; Pradhan et al., 2019; Gu et al., 2020; Míguez et al., 2021). Industrial wastewater contains over 40 heavy metals, including Cu, Zn, Pb, Cd, and Hg, which persist in nature due to their non-biodegradable nature (Zamani et al., 2020). Microalgae absorb heavy metals through specialized surface interactions (Hamed et al., 2017) but exhibit stress symptoms such as slow growth, reduced pigments, and abnormal morphology. Metal ion uptake triggers reactive oxygen species (ROS) accumulation, which, if uncontrolled, disrupts cellular redox balance, damages biomolecules, and can cause cell death (Sun et al., 2018). The extent of damage depends on metal type, concentration, and environmental conditions.

Responses of microalgae to dark and intense light stress

Microalgae, as phototrophic organisms, rely on light for survival and reproduction. Changes in the light regime significantly impact chlorophyll concentration, photosynthesis, and productivity. Prolonged darkness inhibits proteins involved in nitrogen assimilation while stimulating glycolysis and fatty acid synthesis, redirecting cellular carbon and nitrogen to lipid biosynthesis (Bai et al., 2016). Light intensity also affects biomass and nutrient composition. High light increases neutral lipids like TAGs while reducing polar lipids due to oxidative damage (He et al., 2015; Breuer et al., 2013; Carvalho & Malcata, 2005). TAG accumulation rates vary across species such as *Chlorella* sp., *Monoraphidium* sp., *Scenedesmus obliquus*, *Pavlova lutheri*, and *Nannochloropsis gaditana* (Mitra et al., 2015).

Responses of microalgae to oxidative stress

Reactive oxygen species (ROS) are pro-oxidants that trigger oxidative stress. They accumulate from abiotic, anthropogenic, and biological sources, including photosynthesis and enzymatic reactions (Kehrer, 2000). In aerobic organisms, ROS include superoxide anions ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and hydroxyl radicals ($HO\cdot$). Photosynthetic organisms are highly exposed to ROS due to oxygen depletion in the electron transport chain (Chokshi et al., 2017; Gill & Tuteja, 2010; Rezayian et al., 2019). Elevated ROS levels damage nucleic acids, proteins, and lipids, leading to metabolic disorders and potentially cell death (Kehrer, 2000; Gill & Tuteja, 2010).

Anti-cancer activities of microalgae

Most microalgae species are rich in carotenoids, antioxidants known for their antitumor effects (Fleischauer et al., 2003). Many studies have shown that microalgae extracts have various anticancer, antiviral, antimicrobial, antibacterial and anti-inflammatory activities and properties. These algae-derived substances affect various cellular mechanisms such as cytotoxicity, suppression of tumor cell invasion and enhancement of apoptosis of cancer cells (Lee et al., 2013; Farooqi et al., 2012). Extensive research in the field of cell and molecular biology has shown significant and natural antitumor activity of algae compounds (Talero et al., 2015; Kumar et al., 2013). For example, fucoxanthin, a carotenoid found in microalgae, diatoms and brown algae, has shown remarkable cancer properties by inhibiting the growth of malignant cells, activating tumor suppressor genes and disrupting cell cycles while protecting tumor cell apoptosis (Takahashi et al., 2015; Peng et al., 2011). It has also been demonstrated that bioactive substances from microalgae, including lipids, carbohydrates, and phycobiliproteins, have apoptotic and antiproliferative effects on a variety of cancer types (Talero et al., 2015). In a previous study, fucoidan, a sulfated polysaccharide extracted from various microalgae such as *Fucus vesiculosus*, *Sargassum henslowianam*, *Cladosiphon fucoidan* and *Coccophora longsdorfii*, was shown to inhibits angiogenesis and metastasis in human lymphoma, melanoma, colon cancer, breast cancer, lung cancer and human promyeloid leukemia cells by reducing kinase activity and activating caspase-3/7 (Deniz et al., 2017). Microalgae are also rich in docosahexaenoic acid (DHA), a compound known to induce cytotoxicity and upregulate lipid peroxidation. It exhibits antitumor properties due to its effect on the cell nucleus and mitochondria and responds to the resulting stress factors with structural or functional changes that lead to apoptosis (Siddiq & Dembitsky, 2008). In another study, cyanobacterial extracts, which share certain bioactive compounds with microalgae, have shown strong antiproliferative effects and induced DNA damage in cancer cell lines, including colon cancer (Andeden et al., 2018). These findings support the potential anticancer role of microalgal secondary metabolites in breast cancer treatment.

The role of microalgae in breast cancer

Various species of microalgae produce carcinogenic bioactive compounds due to their natural origin such as carbohydrates, peptides, carotenoids, polyphenols and fatty acids, their rapid growth cycle, their ability to survive in a hostile environment, their low toxicity, their diverse bioactivities, their ability to control cellular, subcellular and molecular checkpoints involved in cancer development and progression, as well as their ability to induce autophagy and apoptosis, inhibit telomerase and protein kinases, and these compounds inhibit breast cancer cell proliferation, induce apoptosis and modulate key signaling pathways involved in cancer progression. In addition, the mechanisms of action of these bioactive compounds and their potential synergistic effects with conventional cancer therapies are being investigated. These microalgae offer a promising avenue for the development of alternative and complementary therapies for breast cancer. *In vivo* studies with these microalgae have shown a potent anti-angiogenesis effect on solid tumors as well as a reduction in tumor volume. These bioactive compounds of microalgae have also been investigated in clinical studies on various types of cancer, making them good candidates for the development of antitumor drugs.

In a study investigating the cytotoxic effect and apoptosis mechanism of ethanol extracts from *Chaetoceros calcitrans* on human breast cell lines, it was found that this extract inhibited cell growth in MCF-7 cells by apoptosis induction without cell cycle arrest. It was also observed that this extract induced apoptosis in MCF-7 cells by modulating CDK2, MDM2, p21Cip1, cyclin A2, Bax and Bcl-2 and showed an increase in Bax/Bcl-2 ratio, which activates caspase 7 and activates caspase-dependent pathways (Ebrahimi et al., 2013).

In a study investigating the cytotoxic effect of SRD3 against MCF-7 cell lines *in vitro*, it was found that four different solvent extracts (methanol, ethyl acetate, chloroform and hexane) of *Chlorella* sp. caused the death of MCF-7 cells, although differently for each extract. In addition, the methanol extract was shown to be non-toxic to the control cells, so this extract can be used in the pharmaceutical industry as a good source for the treatment of cancer cells (Sigamani et al., 2019).

Microalgae are known for their bioactive compounds with potential applications such as antimicrobial, anti-aging and anticancer activities. In a study by Akbarizare et al. (2019), the anticancer potential of saponins extracted from *Spirulina platensis* was investigated. After 24-hour treatment with 0.02-2 mg/ml saponin extracted from *S. platensis*, the cytotoxic activity changed in a concentration-dependent manner. The toxicity of saponins was determined as IC50=0.22 mg/ml in MDA-MB-123 cells, while the IC50 value in MCF-7 cells was 0.4 mg/ml. Nowadays, marine microalgae are considered a relatively new and rich source of bioactive compounds used in the nutraceutical and pharmaceutical sectors. In the study conducted by Wali et al. (2020), which investigated the anticancer effect of *Nannochloropsis oculata* extract in

MDA-MB-231 breast cancer cells, it was reported that the viability of the cells decreased depending on the extract concentration and time (400 µg/ml in 24 hours, 300 µg/ml in 48 hours and 200 µg/ml in 72 hours). In addition, it was observed in light microscopy images that the number of cells decreased with increasing concentration in the cells treated with the extract.

In a study by Salem et al. (2020), it was found that the methanol extract of *Chlorella vulgaris*, a type of green algae, showed strong cytotoxic activity against the breast cancer cell line MCF-7 (IC50=15.53 µg/ml).

Nowadays, the main objective of many studies is to screen sources of biologically active compounds that can treat cancer. In a study investigating the anticancer activities of methanol extracts from *Spirulina maxima*, *Chlorella salina*, *Nannochloropsis oceanica* and *Nannochloropsis oculata*, it was reported that the extract from *Spirulina maxima* showed promising activity against breast cancer by causing 75.50±1.76% cytotoxicity at a concentration of 200 µg/ml in MCF-7 cells. This was followed by the extract of *N. oceanica* (46.86±8.15% cytotoxicity) at the same concentration (Elkhateeb et al., 2020). Microalgae are a rich source of polyunsaturated fatty acids. In the study, the cytotoxic effect of the *Chlorella* sp. S14 strain, which has the potential to produce polyunsaturated fatty acids (PUFAs), was investigated on some cancer cells. While the PUFA-rich extract showed no cytotoxic effect on normal cells, the viability of cells from MCF-7 (31.58%) and A549 (62.56%) treated with this extract was significantly reduced. These results demonstrate the potential of PUFA-rich extracts from *Chlorella* sp. S14 to reduce the viability of A549 and MCF-7 cells (Vilakazi et al., 2021).

The most prevalent malignant malignancy in women globally is breast cancer. Conventional medicine has been challenged by drug resistance, toxicity, and the incapacity of present therapies to completely treat breast cancer. As a result, complementary alternative medicine has become popular due to its safety and efficacy. Alateyah et al. (2022) investigated the effects of methanol extract (T1) of *Haematococcus pluvialis* (*H. pulvialis*), a freshwater green microalgae species, on cell growth and migration/invasion in MDA-MB-231 MK cell line and fibroblast control cells. They reported that T1 significantly suppressed the growth of MDA-MB-231 MK cells, inhibited migration and invasion, and induced apoptosis. According to their findings, T1 inhibited invasion and induced apoptosis through the p53/Bax/Bcl2 signaling pathway, which is how it causes cancer. Microalgae-derived bioactive chemicals have been shown to have anti-inflammatory, anti-bacterial, anti-cancer, and antioxidant properties. Basha et al. (2024) performed extractions with three different solvents, namely methanol, acetone and hexane, from the microalgae species *Acutodesmus obliquus* (CN01) and *Desmodesmus perforates* (SP04) isolated and propagated from freshwater. Methanol extracts of *Acutodesmus obliquus* (CN01) and *Desmodesmus perforates* (SP04) showed antiproliferative effects against MCF-7 ranging from 87±1.1271% to 73±0.2744% and 82±0.0236% to 73±0.0423%, respectively.

Soha et al. (2024) investigated how *Spirulina* affects the phosphoinositide 3-kinases/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway, which is important in cancer progression. To this end, a breast cancer model was created using female rats stimulated with 7,12-dimethylbenzanthracene (DMBA), and the antitumor, antioxidant and anti-inflammatory activities of *Spirulina* about breast cancer were evaluated using methods such as comprehensive. The study concluded that *Spirulina* exhibited significant antitumor activity against DMBA-induced breast cancer in female rats and has potential as a therapeutic agent in cancer treatment. *Spirulina* was also shown to possess potent antioxidant properties that contribute to the improvement of oxidative stress markers in the treated rats. This suggests that *Spirulina* may help to alleviate cancer-related oxidative damage. These studies suggest that microalgae extracts have apoptotic and antiproliferative properties on breast cancer cells, which may facilitate the creation of novel medications. However, further research is needed to fully elucidate their mechanisms and clinical applicability in anti-cancer strategies.

Conclusions

Despite the promising potential of microalgae extracts, further research is needed to fully understand their mechanisms and optimize their use in the clinical setting. The integration of these natural compounds into cancer therapy could revolutionize treatment approaches, especially for patients resistant to conventional drugs. All these studies suggest that microalgae extracts can be further investigated as a natural dietary supplement or adjunct therapy in the treatment of breast cancer and additional studies are needed to confirm their efficacy and mechanisms of action.

Author contributions

Solange Kolie: Literature review, figure/table organization, manuscript writing. Pınar Altın-Çelik: Conceptualization, data curation, figure/table organization, critical revision of the manuscript. Hamiyet Dönmez-Altuntaş: Supervision, conceptualization, draft preparation, reference management. Muazzez Derya-Andeden: Conceptualization, manuscript editing, final approval of the version to be published.

Declaration of interests

The authors declare that there is no conflict of interest.

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Sporcularda ergojenik destek olarak aromaterapinin kullanımı

Use of aromatherapy as ergogenic support in athletes

İzem Deniz[1*], Çağla Kızılarslan-Hançer[2]

[1]Bezmialem Vakıf Üniversitesi, Sağlık Bilimleri Enstitüsü, Farmakognozi ve Doğal Ürünler Kimyası Anabilim Dalı, Aromaterapi Programı, İstanbul, Türkiye

[2]Bezmialem Vakıf Üniversitesi, Eczacılık Fakültesi, Farmasötik Botanik Anabilim Dalı, İstanbul, Türkiye

ÖZET

Aromaterapi; bitkilerden elde edilen aromatik uçucu yağların kontrollü kullanımla genel sağlık halini koruyucu, fiziksel, zihinsel ve ruhsal bazı hastalıkların tedavisinde destekleyici görev oynayan, koklama, masaj, oral alımı kapsayan ve bilimsel otoriteler tarafından kabul edilen fitoterapinin alt bir alanıdır. Bu araştırmada; aromaterapinin sporcu performansını desteklemek amacıyla ergojenik destek olarak kullanımını teorik olarak açıklamak hedeflenmektedir. Yapılan araştırma sonucunda sporcularda stres yönetimi, yorgunluk hissiyatının geciktirilmesi, kilo kontrolü, ağrı hissiyatının yönetimi gibi sporcunun performansını dolaylı yollardan arttırmak, çeşitli yaralanmaların tedavisini desteklemek ve toparlanma süresini hızlandırmak amacıyla aromaterapiden faydalanılabileceği sonucuna ulaşılmıştır. Ancak uçucu yağların kullanımı esnasında güvenli doz aralığı ve kullanım şekillerine, depolama kurallarına dikkat edilmelidir. Eğer iki ya da daha fazla uçucu yağ karışımı hazırlanacaksa, uçucu yağların birbirleri ile etkileşimi konusunda dikkatli olunmalıdır.

Anahtar kelimeler: Aromaterapi, sporcu, sporcu performansı, ergojenik destek

ABSTRACT

Aromatherapy is a sub-field of "Phytotherapy" that is accredited by scientific authorities, which aims to protect general medical condition with the controlled usage of aromatic essential oils originated from the herbs. It acts as a supportive agent in the process of treating some of physical, mental and psychological illnesses, by the methods of olfactory stimulation, physical massage and oral intake. According to research done, it is concluded that aromatherapy may be applied for increasing the performance of the athletes by indirect methods such as stress management, delaying the feeling of fatigue, weight control, mechanisms to cope with pain, for supporting the treatment of various injuries, and to fasten the process of healing. However, during the use of essential oils, attention should be paid to the safe dose range and usage patterns, as well as the storage rules. If a mixture of two or more essential oils is to be prepared, care should be taken about the interaction of essential oils with each other.

Keywords: Aromatherapy, athlete, athlete performance, ergogenic support

***İletişim:**
dytizemdeniz@gmail.com

ORCID iD:
0000-0002-7497-2844

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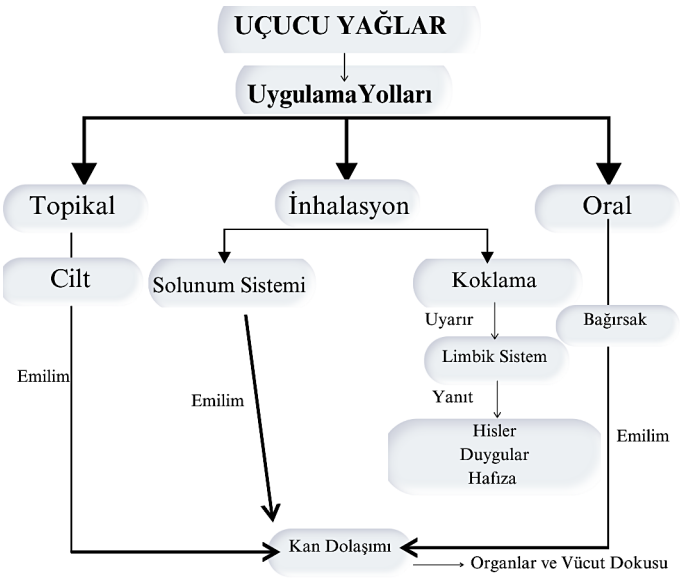
Giriş

Aromaterapi; bitkilerden elde edilen aromatik uçucu yağların kontrollü kullanımla genel sağlık halini koruyucu, fiziksel, zihinsel ve ruhsal bazı hastalıkların tedavisinde destekleyici görev oynayan, koklama, masaj, oral alımı kapsayan ve bilimsel otoriteler tarafından kabul edilen fitoterapinin bir alt alanıdır (Altıntaş ve Kartal, 2021; Gültekin, 2020; Tayfun, 2019). Aromaterapi kelimesini ilk kez kullanan Fransız kimyacı Rene-Maurice Gattefose'dir. Kelime kökeni eski Yunanca'daki therapeia = bakım, tedavi ile aroma = koku kelimelerine dayanmaktadır (Altıntaş ve Kartal, 2021).

Bitkilerin çeşitli bölgelerinden (kök, gövde, çiçek, yaprak vb.) çeşitli yöntemlerle elde edilen ve sekonder metabolitler olan uçucu yağlar temel olarak terpenlerden (5 karbonlu izopren ünitesi) oluşmaktadır. Uçucu yağlarda bulunan terpenler, kendi içlerinde başlıca monoterpen, seskiterpenler ve bunların oksijenli türevlerinden monoterpenoid, seskiterpenoid ve diterpenler olarak ayrılmaktadır. Oda sıcaklığında genelde sıvı formda bulunan, genellikle soluk sarı veya sarı renkli ve sudan hafif bir yapıya sahip kokulu bileşikler olan uçucu yağların bileşiminde terpenlere ek olarak alifatik alkoller, esterler, aldehitler, ketonlar, eterler ve bazı basit fenolik bileşikler bulunabilmektedir (Altıntaş ve Kartal, 2021).

Uçucu yağlar; antiviral, antifungal, antibakteriyel gibi etkileriyle ön plana çıkarken bazı duyguları yatıştırma, spazm çözme, kan dolaşımı üzerine etki etme, savunma sistemini destekleme, zihni açma ya da yatıştırma gibi etkileri de bulunmaktadır (Gültekin, 2020). Aromaterapinin uygulanma yöntemleri; inhalasyon, topikal ve oral kullanımdır (Şekil 1).



Şekil 1. Uçucu yağların uygulama yolları (Gnatta vd., 2016)

İnhalasyon yöntemiyle uçucu yağlardaki moleküller, burundaki koku reseptörlerine ulaşır ve bağlanır. Reseptörlerde bu moleküller elektriksel impulslara dönüşerek olfaktör yolun verdiği dallarda limbik sisteme iletilerek duygu ve davranışı etkiler. Ardından temporal ve frontal loba giden iletiler algılanır ve yorumlanır. Oluşan yanıt, beynin diğer bölümlerine ve vücuda gönderilir. Bu mesajlar; rahatlatıcı, sedasyon ve uyarıcı etkileri oluşturur (Cambaz Kurt ve Çankaya, 2021).

Topikal uygulama yönteminde ise uçucu yağlar, derideki gözeneklerden absorbe olur ve kan dolaşımına katılarak tüm vücuda ulaşırlar (Cambaz Kurt ve Çankaya, 2021).

Aromaterapi; temelde medikal, estetik, psikiyatrik, holistik olarak 4 uygulama alanı olmakla birlikte hayvan sağlığının korunmasında, hayvan yemlerinde ve gıda endüstrisinde ise koruyucu, aroma verici, renklendirici olarak kullanılmaktadır (Cambaz Kurt ve Çankaya, 2021).

Aromaterapi; uçucu yağların kullanımı yolu ile zihinsel ve fiziksel rahatlama sağlamaktadır. Bu makalenin amacı; uçucu yağların sporcular üzerindeki potansiyel olumlu etkilerini araştırarak aromaterapinin sporcular için ergojenik bir destek olarak kullanımını değerlendirmektir.

1. Sporcularda stres yönetiminde aromaterapi

Sporcular sezon içerisinde antrenman yoğunluğu, müsabaka baskısı ve performans kaygısı gibi nedenlerle yüksek stres altında olabilmektedirler. Uzun süreli stres, sporcularda performansın düşmesine, motivasyon kaybına neden olabilmektedir. Sporcularda stres düzeylerinin kontrol altında tutulması; sporcuların performanslarının arttırılmasına yardımcı olabilmektedir (Ünal, 2023). Aromaterapi, sporcularda stres yönetimi için doğal, etkili ve güvenli bir yöntem olarak öne çıkmaktadır. Aromaterapi sporcularda stresin performans üzerindeki olumsuz etkilerini azaltarak dengeli ve odaklanmış bir zihin durumunu desteklemektedir.

1.1. Lavanta uçucu yağı: Stres yönetiminde en yaygın kullanılan uçucu yağlardan biri olan lavanta (*Lavandula* spp.) uçucu yağının güçlü bir sakinleştirici özelliğe sahip olduğu bilinmektedir (Ebrahimi vd., 2022). Lavanta yağının özellikle hipokampüs ve amigdala olmak üzere limbik sisteme etki ederek kişilerde rahatlama sağladığı ve stres düzeylerinin düşürülmesine yardımcı olduğu bilinmektedir. Öte yandan lavantanın gama-aminobütirik asit (GABA) üzerine etkileri olduğu ve amigdaladaki GABA düzeyini arttırdığı bilinmektedir (Kehr vd., 2010). Lavanta uçucu yağının stres düzeylerine etkisini inceleyen geniş çaplı bir

meta analiz çalışması sonucunda lavantanın bireylerin stres seviyelerini önemli ölçüde azalttığı gösterilmiştir (Ghavami vd., 2022).

1.2. Bergamot uçucu yağı: Bergamot (*Citrus bergamia*) uçucu yağının kişilerde kortizol ve anksiyete seviyelerini düşürücü etkisi olduğu bilinmektedir (Watanabe, vd., 2015). Bergamot uçucu yağının; hipokampüsdeki GABA seviyelerini önemli ölçüde arttırıcı ve akut strese karşı kortikosteron düzeylerini düşürücü etkisi olduğundan, kişilerde stres ve kaygıyı azaltmak için yaygın olarak kullanılmaktadır (Saiyudthong ve Marsden, 2011). Bergamot uçucu yağının inhalasyon yolu ile uygulanması kişilerde anksiyete seviyelerini düşürmekte ve olumlu duyguların artmasını desteklemektedir (Han vd., 2017; Saiyudthong ve Marsden, 2011; Watanabe vd., 2015)

1.3. Ylang-ylang uçucu yağı: Ylang-ylang (*Cananga odorata*) uçucu yağının kan basıncını düşürerek sakinleştirici ve rahatlatıcı etkisi olduğu bilinmektedir (Jung vd., 2013).

1.4. Limon uçucu yağı: Yapılan bir çalışmada limon (*Citrus limon*) uçucu yağının intraperitoneal uygulamasının serum kortikosteron ve serebral monoamin seviyelerinin yükselmesini inhibe ettiği, stres üzerinde hafifletici etkisi olduğu gözlemlenmiştir. Limon, okaliptüs, çay ağacı, nane uçucu yağlarından 4:2:2:1 oranlarında oluşturulan bir karışımın; inhalasyon yoluyla uygulamasının stres ve depresyon seviyelerini düşürdüğü bilinmektedir (Lee vd., 2017).

1.5. Frankincense uçucu yağı: Frankincense (*Boswellia carteri*) uçucu yağı; jojoba yağı ile seyreltilip topikal olarak uygulandığında, plazma kortikosteron seviyeleri üzerine limon yağı ile benzer etkiyi gösterdiği ve plazma glutatyon (GSH) seviyeleri üzerinde düşürücü etkiye sahip olduğu bildirilmiştir (Okano vd., 2019).

1.6. Turunç uçucu yağı: Turunç (*Citrus aurantium*) uçucu yağına %2,5 ve %5 konsantrasyonlarında 7 dakika boyunca maruziyetin depresif ruh hali üzerine olumlu etkileri olduğu, sakinleştirici ve rahatlatıcı etkileri olduğu raporlanmıştır (Leite vd., 2008).

1.7. Biberiye uçucu yağı: Biberiye (*Rosmarinus officinalis*) uçucu yağının kişilerde anksiyete ve depresyon seviyelerini düşürdüğü bilinmektedir (Alvarado-García vd., 2023).

2. Sporcularda yorgunluk hissiyatının geciktirilmesinde aromaterapi

Yorgunluk, sporcu performansını sınırlayan ve uzun süreli antrenman veya müsabakalarda ortaya çıkabilen önemli bir faktör olmakla birlikte yorgunluk hissiyatının artmasına bağlı olarak spor performansı olumsuz etkilenebilmektedir (Dambroz vd., 2022). Aromaterapi, yorgunluk hissini azaltarak dayanıklılığı arttırmak amacıyla kullanılabilmektedir. Buna ek olarak uçucu yağların sporcularda sinir sistemini uyararak enerji seviyelerini arttırabildiği bilinmektedir. Aromaterapinin sporcularda hem fiziksel hem de zihinsel yorgunluk üzerine olumlu etkileri bulunmaktadır. Aromaterapi ile sporcularda yorgunluk hissiyatı geciktirilerek sporcuların performanslarının artışı desteklenebilmektedir.

2.1. Nane uçucu yağı: Nane (*Mentha piperita*) yağının; bileşiminde bulunan mentol sayesinde, canlandırıcı ve enerji verici etkisi bulunmaktadır. Yapılan çalışmalarda nane uçucu yağının; kan laktat seviyelerini düşürdüğü, karbonhidrat metabolizmasını iyileştirdiği, sistolik kan basıncı ve kalp atım hızını düşürdüğü saptanmıştır (Meamarbashi ve Rajabi, 2013). Fareler üzerinde yapılan bir çalışmada; *Citrus sinensis*, *Mentha piperita*, *Syzygium aromaticum* ve *Rosmarinus officinalis* uçucu yağları ile hazırlanan bir karışımın egzersiz sonrası inhalasyon yoluyla 3 gün boyunca uygulamasının kandaki laktik asit, üre nitrojeni, malondialdehit seviyelerini azalttığı; glutatyon peroksidaz seviyelerini düşürdüğü ve kan şekerini arttırdığı gözlemlenmiştir (Li vd., 2017). Yapılan bir başka çalışmada 21 gün boyunca *Santalum album*, *Citrus aurantium*, *Citrus limonum*, *Styrax benzoin*, *Citrus paradisi*, *Mentha piperata*, *Acorus tatarinowii*, *Rhodiola crenulata* ve *Camellia sinensis* uçucu yağlarından hazırlanan bir karışımın 21 gün boyunca inhalasyon yöntemiyle uygulanmasının merkezi yorgunluğu azalttığı gözlemlenmiştir (Han vd., 2018). 12 gün boyunca 0,05 oranında nane uçucu yağı eklenmiş maden suyu tüketiminin, solunum ventilasyonunu, solunum hızını, solunum verimliliğini ve enerji harcamasını önemli ölçüde arttırdığı gözlemlenmiştir (Durusoy ve Göze Ulusal, 2007). Sıçanlar ile yapılan bir başka çalışmada ise nane yağının; yüzme antrenmanı sırasında yorgunluk süresini geciktirdiği ve dayanıklılık egzersizine bağlı oluşan oksidatif hasarı azalttığı saptanmıştır (Zhang vd., 2023). McKenzie ve arkadaşlarının yürüttüğü bir çalışmada; nane uçucu yağının inhalasyon yöntemi ile uygulamasının; koşu esnasındaki kalp atım hızını önemli ölçüde azalttığı saptanmıştır (MacKenzie ve Hedge, 2005). Ayrıca nane inhalasyonunun aerobik performans ve reaksiyon süresi ile anlamlı bir ilişkisi olduğu bilinmektedir (Shahresfangreh, 2011).

2.2. Biberiye uçucu yağı: Li ve arkadaşlarının yürüttüğü bir çalışmada *Citrus sinensis*, *Mentha piperita*, *Syzygium aromaticum* ve *Rosmarinus officinalis*'den oluşan bir uçucu yağ karışımının inhalasyon yöntemi ile uygulanmasının, sıçanlarda fiziksel yorgunluk önleyici etki gösterdiği raporlanmıştır (Li vd., 2017). Boks sporcuları ile yapılan bir çalışmada biberiye uçucu yağının antrenman sonrası masaj yapılarak topikal uygulamasının sporcularda; kreatin fosfokinaz, laktat dehidrojenaz, kortizol, adenokortikotropik hormon düzeylerini anlamlı olarak azalttığı gözlemlenmiştir (Tianlong ve Sim, 2019).

2.3. Turunçgil (*Citrus* spp.) uçucu yağları: Bergamot uçucu yağının oksidatif stresin inhibisyonu, kas yaralanmasının korunması ve glikoza bağlı enerji tedarikinin arttırılması yolu ile egzersize bağlı yorgunluğun azaltılmasında etkili olduğu bilinmektedir (Tian vd., 2022). Portakal (*Citrus sinensis*) uçucu yağının egzersiz öncesinde inhalasyon yöntemi ile uygulanmasının; atletik performansı ve akciğer fonksiyonları iyileştirmektedir (Jaradat vd., 2016). Boks sporcuları ile yapılan bir çalışmada ise tatlı limon (*Citrus aurantifolia*) uçucu yağının masaj yolu ile uygulamasının sporcularda laktik asit ve ağrı düzeylerini düşürdüğü saptanmıştır (Harahap vd., 2023).

3. Sporcu yaralanmalarında aromaterapi

Aynısefa (*Calendula officinalis*) bitkisinden maserasyon yoluyla elde edilen yağın immünomodülatör ve antimikrobiyal etkili olduğu; kolajen ve glikoprotein sentezini arttırarak yara tedavisinde etkili olduğu ve burkulma tedavisinde kullanılabileceği bilinmektedir (Başer, 2009; Durusoy ve Göze Ulusal, 2007). Yaraya tek başına uygulanan sarı kantaron (*Hypericum perforatum*) maserasyon yağı ile *H. perforatum*, *Origanum majorana*, *Origanum minutiflorum* ve zeytinyağından birebir oranlarda hazırlanan karışımın yara iyileştirici özellikleri kıyaslandığında karışımın yara iyileştirici etkisinin daha fazla olduğu gözlemlenmiştir (Süntar vd., 2011). Aloe vera yağı; hyaluronik asit ve dermatan sülfat sentezini, tip 3 kolajen yapımını arttırarak yara iyileşmesini desteklemektedir ve iyi bir antiseptiktir (B. Türsen ve Ü. Türsen, 2014). Çay ağacı (*Melaleuca alternifolia*) yağının; hücre yoğunluğu, damarlanma ve kolajen sentezini arttırarak yara iyileşmesini desteklediği ve antimikrobiyal özelliğinden dolayı yara temizliğinde kullanılabileceği bildirilmiştir. Çay ağacı yağı antioksidan etkisi ile inflamasyon nedeniyle aşırı üretilen oksidasyon radikallerinin olumsuz etkilerini önlemeye yardımcı olmaktadır (Sürme ve Çürük, 2020).

Artemisia judaica yara tedavisinde etkili olduğu bilinen bir diğer bitkidir (Mohammed vd., 2022). Yapılan çalışmada, *Olea europaea*, *Nigella sativa* ve *Rosmarinus officinalis* yağlarından hazırlanan karışımın yara iyileşmesinde etkili olduğu ve antiviral etki gösterdiği bildirilmiştir (Yanar, 2015). Lavanta yağı; yara iyileşmesinde etkili olduğu bilinen bir diğer aromatik yağdır. Ancak açık yaraya uygulama kontraendikedir (Demir ve Satılmış, 2019). Ada çayının (*Salvia fructicosa*) antimikrobiyal ve yara iyileştirici etkisi bulunmaktadır (Tarım ve Orman Bakanlığı, 2025).

4. Sporcularda bağ doku yaralanmalarında aromaterapi

Sporcularda bağ doku yaralanmaları, özellikle yoğun antrenman ve müsabakalar sırasında kaslar, bağ dokular ve eklemlerin olağandan fazla bir kuvvet ile karşılaşması sonucu dayanıklılık sınırlarının aşılması nedeniyle ortaya çıkan ve sıkça karşılaşılan sorunlardır (Kolukısa ve Kaya, 2023). Kas zedelenmeleri, tendon ve ligament yaralanmaları gibi akut ya da kronik durumlar, sporcuların performansını olumsuz etkileyebilir ve iyileşme süreci uzun sürebilir (Bahr ve Mæhlum, 2004; Özdilek, 2019). Modern tıp tedavilerine ek olarak aromaterapi, bu yaralanmaların tedavisinde tamamlayıcı bir yöntem olarak kullanılabilmektedir.

4.1. Sarı kantaron yağı: Aşil tendonu kopmasına etkisinin araştırıldığı fareler üzerinde yapılan bir çalışmada; günde 300 mg sarı kantaron yağı içeren kapsül alan grup ile sarı kantaron ve Tendoflex kapsülü alan grupta; 2., 3. ve 4. haftalarda iyileşme ve onarım süreçleri üzerine olumlu etki gözlemlenmiş ve bu etki, tip 1, 3 kolajen ekspresyonunu arttırmasıyla açıklanmıştır (Tuncer vd., 2021).

4.2. Alacalı zencefil uçucu yağı: Tedavi grubuna tenatomi sonrası 0,3 ml/kg/gün oranında alacalı zencefil (*Alpinia zerumbet*) uçucu yağının 3, 14, 30, 90 gün topikal uygulamasının 14. ve 30. günlerinde tendon hücreleri ve fibroblast sayılarında önemli farklılıklar olduğu, 30 gün sonunda fibroblast sayısının azaldığı, 90 gün sonunda ise yüksek oranda tip 1 kolajen liflerin oluşmasına önemli ölçüde katkı sağladığı bildirilmiştir (Santos-Júnior vd., 2017).

4.3. Aynısefa uçucu yağı: %4 konsantrasyonunda *Calendula officinalis* uçucu yağı içeren kremin, 5 gün boyunca topikal uygulamasının tendonlardaki kolajen içeriğinin bir göstergesi olan hidroksiprolin konsantrasyonlarını arttırdığı, tip 1 kolajen sayısında

anlamlı bir fark olmadığı, artan kolajen tipinin tip 3 kolajen olabileceği bildirilmiştir (Aro vd., 2015).

4.4. Biberiye uçucu yağı: Biberiye, sardunya, okaliptüs, papatya uçucu yağlarından karışım şeklinde hazırlanan masaj yağının; hipoaktif derin tendon refleksleri, disestezi, parestezi, nöropatik ağrı, motor zayıflık gibi periferik semptomların azaltılmasında etkili olduğu bilinmektedir (Nasiri vd., 2021).

5. Sporcularda ağrı hissiyatı ve aromaterapi

Sporcular yoğun antrenman ve müsabakalar esnasında ağrı hissiyatı ile karşı karşıya kalabilmektedirler. Bu ağrılar ise spor performansını ve günlük yaşamı olumsuz etkileyebilmektedir. Aromaterapi, sporcularda ağrı hissini hafifletmek ve iyileşme sürecini desteklemek için etkili bir tamamlayıcı yöntem olarak kullanılabilmektedir.

Şam gülü (*Rosa damascena*) uçucu yağının inhalasyon yoluyla uygulamasının ağrı hissiyatının azaltılmasında etkili olduğu raporlanmıştır (Ahmadnejad-Asl-Gavgani vd., 2022).

Tanacetum balsamita, bergamot ve karvon içeren uçucu yağların kas spazmı giderici etkileri olduğu bilinmektedir. (Ahmadnejad-Asl-Gavgani vd., 2022; Lenardao vd., 2016; Rombala vd., 2022). Bergamot uçucu yağı aynı zamanda antinosiseptif etki göstermektedir (Lenardão vd., 2016). *Thymus algeriensis* ve *Artemisia alba* uçucu yağları, güçlü analjezik etki gösteren yağlardır. Bu iki yağın birlikte kullanımı sinerjik etki oluşturabilmektedir (El Quahdani vd., 2021).

Yapılan çalışmada kafur ağacı (*Cinnamomum camphora*) uçucu yağının 6 gün boyunca topikal uygulamasının prostaglandin, TPRM8 seviyelerini düşürdüğü ve analjezik etki gösterdiği raporlanmıştır (Xiao vd., 2021). *Citrus limon* uçucu yağı antinosiseptif ve analjezik etkiye sahiptir. Yapılan çalışmada limon uçucu yağının 50mg/kg, 100mg/kg, 150 mg/kg oral doz uygulamasının kıvranma sayısını önemli ölçüde azalttığı gözlemlenmiştir (Campêlo vd., 2011). 0,1 ml/kg doz karanfil yağı uygulamasının, analjezik etki gösterdiği bildirilmiştir (Halder vd., 2012).

Hypericum perforatum maserasyon yağının günde 5 mg/kg uygulamasının uzun süreli analjezik etki sağladığı ve antinosiseptif etkisi olduğu bildirilmiştir (Ersoy ve Özkan, 2019).

Lavandula angustifolia, *Achillea millefolium*, *Laurus nobilis*, *Melissa oficinalis*, *Nigella sativa*, *Ocimum basilicum*, *Pimpinella anisum* antinosiseptif etki gösteren diğer uçucu yağlardır (Lenardão vd., 2016).

Biberiye uçucu yağının kas spazmlarının iyileştirilmesinde olumlu etkileri olduğu bilinmektedir. Yapılan bir çalışmada; biberiye uçucu yağının antrenmandan 48 saat sonrasında, kas hasarının bir göstergesi olan serum kreatin kinaz değerlerinde olumlu etkisi olduğu saptanmıştır (Rezaee vd., 2020). Biberiyenin analjezik ve anti-inflamatuar özellikleri sayesinde bireylerde kas ağrılarını ve kas spazmlarını hafiflettiği bilinmektedir (Mohammed vd., 2022).

6. Sporcularda kilo kontrolünde aromaterapi

Sporcularda kilo kontrolü, spor performansının en üst düzeye çıkarılabilmesi, dayanıklılık performansının artması ve sakatlık riskinin azaltılabilmesinde önemli rol oynamaktadır (Richmond vd., 2016; Wilmore ve Costill, 2004). Aromaterapi iştahı baskılayıcı, kan şekerini düzenleyici, lipolizi arttırıcı etkileri ile sporcularda kilo kontrolüne katkı sağlayabilmektedir.

6.1. Limon uçucu yağı: *Citrus limon* beyaz yağ dokusunu innerve eden sempatik sinirlerin aktivasyonunu destekler ve lipolizi arttırarak vücut ağırlığının artışının baskılanmasına yardımcı olur. 30 gün boyunca günde 400 mg/kg dozunda d-limonen uygulamasının, LDL-kolesterolü düşürdüğü, lipid birikimini önlediği ve kan şekeri seviyesini etkilediği bildirilmiştir. Aynı çalışmada, d-limonen diyet takviyesinin, karaciğer ve pankreasın patolojik değişimini düzelttiği ve obezitenin önlenmesine yardımcı olabileceği raporlanmıştır. D-limonen'in; 50, 100 ve 200 mg/kg vücut ağırlığı dozlarında oral yoldan 45 gün boyunca uygulandığı bir araştırmada, kan şekerinin kademeli olarak düştüğü ve maksimum etkinin 100 mg/gün doz uygulamasında olduğu görülmüştür (Dosoky ve Setzer, 2018; Klimek-Szcykutowicz vd., 2020).

6.2. Acı portakal (turunç) uçucu yağı: Acı portakal uçucu yağının kilo kaybı üzerine olumlu etkileri olduğu bilinmektedir. Yapılan çalışmalarda *C. aurantium* özütü ve bileşeni *p*-synephrine'in kilo kaybı üzerine etkileri incelenmiş olup *C. aurantium* özütünün tek başına veya diğer bileşenlerle birlikte kullanıldığında kalp atış hızında veya kan basıncında artış veya elektrokardiyografik verilerde, serum kimyasında, kan hücresi sayımlarında veya idrar analizinde herhangi bir olumsuz etki gözlemlenmemiştir. Bunula birlikte *p*-synephrine'in 6-12 hafta boyunca tüketiminin; metabolizma hızını, enerji harcamasını arttırdığı ve kilo kaybını desteklediği raporlanmıştır (Stohs vd., 2012). Sıçanlarla yapılan bir başka çalışmada ise 10 gün boyunca günde 5.6 mg/kg *C. aurantium* tüketiminin viseral yağ kütlesinde %30'luk bir düşüşe yardımcı olduğu bildirilmiştir (Verpeut vd., 2013).

6.3. Zencefil uçucu yağı: Zencefil (*Zingiber officinale*) uçucu yağının obezite üzerine etkisinin incelendiği bir çalışmada; farelere 12 hafta boyunca 12,5mg/kg, 62,5 mg/kg, 125 mg/ kg dozlarında zencefil uçucu yağı verilmiş ve yüksek yağ içerikli bir diyet uygulanmıştır. Araştırmanın sonucunda zencefil yağının yüksek yağ içerikli diyete bağlı gelişen obezitede kilo alımını kademeli olarak düşürdüğü, 62,5 mg/kg ve 125 mg/kg doz uygulamasının hepatik lipid birikimini ciddi oranda azalttığı gösterilmiştir (Lai vd., 2016).

6.4. Sarımsak uçucu yağı: Sarımsak (*Allium sativum*) uçucu yağı ile yapılmış benzer bir çalışmada, 12 hafta boyunca 25 mg/kg, 50 mg/kg, 100 mg/ kg doz uygulamasının yüksek yağlı diyetin neden olduğu vücut ağırlığı, vücut yağ dokusu ağırlığının artışını ve serum biyokimyasal parametrelerini azaltarak antihiperlipidemik ve antiobezite etki gösterdiği ve 50 mg/kg ve 100 mg/kg doz uygulamasının karaciğerdeki proinflamatuar sitokin salınımını inhibe ettiği bildirilmiştir (Lai vd., 2014).

6.5. Tatlı pelin otu uçucu yağı: *Artemisia annua* ile *in vitro* ortamda yapılan bir araştırmada, obeziteyle ilişkili olan PPAR-y, C/EBR-a, SREBP-1c, FAS ve ACC seviyelerini azalttığı bildirilmiştir (Hwang vd., 2016).

6.6. Diğer turunçgil (*Citrus* spp.) uçucu yağları: *Citrus aurantifolia* uçucu yağının gıda alımını azalttığı ve kilo vermede etkili olduğu bilinmektedir (Anaashari, vd., 2010). Yapılan bir araştırmada *C. sinensis* uçucu yağının deri altı yağ dokusunun lipogenezini desteklediği, kilo kaybına yardımcı olduğu gösterilmiştir. *C. paradisi* uçucu yağının inhalasyon uygulamasının; beyaz ve kahverengi yağ dokusunu innerve eden sempatik sinirlerin aktivitesini ve adrenal bezlerin, böbreklerin aktivitesini arttırarak lipolizi arttırdığı ve iştahı azalttığı raporlanmıştır (De Blasio vd., 2021).

6.7. Citronella uçucu yağı: Citronella (*Cymbopogon nardus*) yağının inhalasyon uygulamasıyla iştahı azalttığı raporlanmıştır (Baturaba vd., 2015).

6.8. Rezene uçucu yağı: Rezene (*Foeniculum vulgare*) uçucu yağının inhalasyon uygulaması lipid metabolizmasındaki bozuklukları iyileştirmede etkilidir (Hong vd., 2022).

6.9. Patchouli uçucu yağı: Patchouli (*Pogostemon cablin*) uçucu yağının inhalasyon uygulamasıyla vücut ağırlığının azaldığı, serum leptin seviyelerinin düştüğü ve iştahın azaldığı bildirilmiştir (De Blasio vd., 2021).

6.10. Kekik uçucu yağı: Yüksek karvakrol içerikli kekik (*Origanum* spp.) yağının iyi bir anti-obezite özellik gösterdiği, obez kişilerde hiperkolesterolemi ve inflamasyonu azalttığı bilinmektedir (De Blasio vd., 2021).

6.11. *Cinnamomum osmophloeum* uçucu yağı: *Cinnamomum osmophloeum* uçucu yağının; kan trigliserit düzeylerini azalttığı, kilo kaybına yardımcı olduğu, adipositlerde lipid birikimini önlediği böylece potansiyel bir anti-obezite etkiye sahip olduğu bildirilmiştir (De Blasio vd., 2021).

7. Sporcularda atlet ayağı tedavisinde aromaterapi

Sporcular, yoğun terleme ve hijyen koşullarından dolayı mantar enfeksiyonları gibi cilt problemleri ile karşılaşabilmektedirler. Atlet ayağı, sporcularda görülen mantar enfeksiyonlarından (García-Lira vd., 2024) biri olmakla birlikte tedavisinde uçucu yağlardan faydalanılabilmektedir.

Atlet ayağı (tinea pedis); ılık ve nemli ortamlarda yetişen dermatofit adı altında toplanan mantarının yol açtığı bir mantar enfeksiyonudur. Çay ağacı uçucu yağı; atlet ayağı tedavisinde kullanılabilmektedir. %2 veya %50 konsantrasyonlarında çay ağacı uçucu yağı içeren kremlerin; 4 hafta boyunca günde 2 kez ilgili bölgeye uygulanmasının; iltihaplanma, yanma, kaşıntı gibi atlet ayağı semptomlarını azalttığı, atlet ayağına neden olan dermatofitlere karşı güçlü bir inhibitör etkisi olduğu raporlanmıştır (Bilgi, 2022; Göçmen, 2020; Satchell vd., 2002).

8. Sporcularda aromaterapi uygulamalarında uçucu yağların etkin ve güvenli kullanımı: Dikkat edilmesi gereken hususlar

Aromaterapide; olası toksik etkilerin belirlenebilmesi amacı ile genotoksisite/karsinojenite, üreme ve gelişme toksisitesi, tekrarlı doz toksisitesi (NOAEL - No observed adverse effect level), deri duyarlılığı, iritasyon, solunum toksisitesi, fototoksisite ile ilişkin verilerin değerlendirilmesi gerekmektedir. Tekrarlı doz toksisitesi çalışmaları sonucunda hiçbir toksik etkinin görülmediği en yüksek doz NOAEL değeri olarak ifade edilir. Aromaterapide güvenli maruz kalma sınırı ise MOE (Margin of exposure) değeri ile ifade edilmekte ve bu değer NOAEL değerinin maruz kalınan miktara bölünmesi ile hesaplanmaktadır. Bu

hesaplama sonucunda elde edilen değerin 100 ve üzerinde olması o maddenin güvenli olduğunu göstermektedir (Altıntaş ve Kartal, 2021).

Uçucu yağların birçoğu genel olarak güvenli (GRAS - Generally recognized as safe) kabul edilmekte ve Amerikan Gıda ve İlaç Dairesi (FDA - U.S. Food and Drug Administration) tarafından gıdalarda kullanımı kabul edilerek gıda kimyasalları kodeksinde yer almaktadır. Ancak bu uçucu yağların da çeşitli faktörlere bağlı olarak toksik etki gösterebileceği unutulmamalıdır (**Tablo 1.**). Yüksek doz maruziyeti ya da toksik bileşen mevcudiyeti, bireysel hassasiyet, ürünlerin birbiri ile etkileşimleri, yanlış kullanım gibi faktörler uçucu yağlarda toksik yanıt oluşturabilmektedir (Altıntaş ve Kartal, 2021). Uçucu yağlarda en yaygın olarak gözlemlenen yan etkiler; göz, mukoza zarı, cilt tahrişi, aldehit ve fenol içeren yağlara karşı hassasiyettir (Ali vd., 2015).

Özellikle topikal aromaterapi uygulamalarında en önemli güvenlik endişesi olan hassasiyet riski; bir kişinin bir uçucu yağı defalarca yeteri kadar seyreltilmeden kullanımı sonucu gelişebilen ve geri döndürülemez bir alerjik reaksiyona sebep olabilir (Sheppard-Hanger ve Hanger, 2015). Bazı uçucu yağların topikal kullanımda kişilerde hassasiyet geliştirebileceği bilinmekte ve bu tür yağların topikal kullanımından kaçınılmalıdır. Aromaterapi alanındaki güvenlik uzmanı Robbert Tisserand; uçucu yağların seyreltilmesinin önemini vurgulamış ve uçucu yağların seyreltilerek kullanılmasının kişilerde tahriş, hassasiyet ve fotosensitizasyon gibi cilt reaksiyonlarının önlenmesinde kritik bir rol oynadığını belirtmiştir (Sheppard-Hanger ve Hanger, 2015). Genel olarak taşıyıcı yağlarla seyreltilen uçucu yağlar maksimum konsantrasyonun %5'ini geçmemelidir (S. Price ve L. Price, 2011) (**Tablo 2.**).

Tablo 1. Bazı uçucu yağların olası toksik etkileri (S. Price ve L. Price, 2011)

Uçucu yağ bitkisi	Toksik etki
Achillea millefolium	**Nörotoksik**
Cedrus atlantica	
Cinnamomum camphora	
Eucalyptus dives	
Hyssopus officinalis	
Mentha pulegium	
Mentha spicata	
Tagetes glandulifera	
Cinnamomum cassia	**Ciltte tahriş**
Cinnamomum verum cortex	
Cinnamomum verum folium	
Cuminum cyminum	
Cymbopogon citratus	
Origanum heracleoticum	
Origanum vulgare	
Syzygium aromaticum flos	
Syzygium aromaticum folium	
Thymus serpyllum	
Thymus vulgaris	
Angelica archangelica	**Fototoksik**
Carum carvi	
Cinnamomum cassia	
Cinnamomum verum	
Citrus aurantifolia	
Citrus aurantium var. *amara*	
Citrus bergamia	
Citrus limon	
Cuminum cyminum	
Levisticum officinale	
Aloysia triphylla	
Melissa officinalis	
Ruta graveolens	
Zingiber officinale	

Uçucu yağ bitkisi	Toksik etki
Cananga odorata	**Vücutta hassasiyet**
Cinnamomum cassia	
Cinnamomum verum	
Citrus bergamia	
Costus speciosus	
Ficus carica	
Inula helenium	
Aloysia triphylla	
Pimpinella anisum	
Syzygium aromaticum	

Tablo 2. Bazı uçucu yağlar ve güvenli maksimum konsantrasyon oranları (S. Price ve L. Price, 2011)

Uçucu Yağ Adı	Güvenli Maksimum Konsantrasyon
Angelica root uçucu yağı (*Angelica archangelica*)	% 0.8
Bergamot uçucu yağı (*Citrus bergamia*)	% 0.4
Cassia uçucu yağı (*Cinnamomum cassia*)	% 0.2
Cinnamon bark uçucu yağı (*Cinnamomum verum*)	% 0.2
Udi hindi uçucu yağı (*Costus speciosus*)	% 0.0
Cumin uçucu yağı (*Cuminum cyminum*)	% 0.4
Ficus carica uçucu yağı	% 0.0
Lemon uçucu yağı (*Citrus limon*)	% 2.0
Lime uçucu yağı (*Cistus aurantifolia*)	% 0.7
Sedef otu uçucu yağı (*Ruta graveolens*)	% 0.8
Kara ardıç uçucu yağı (*Juniperus sabina*)	% 0.0
Limon otu uçucu yağı (*Aloysia citrodora*)	% 0.0

Terapötik etki amacı ile kullanılacak olan uçucu yağların; farmakope standartlarına uygun olması, bu ürünlerin kalitesi ve kullanım güvenliği açısından önem arz etmektedir. Ayrıca kullanılacak olan uçucu yağların elde edildiği bitkisel materyalin drog kalitesinde olması, uçucu yağın kalitesini belirleyen önemli bir faktördür. Uçucu yağların güvenli kullanımında kullanılacak olan yağın fiziksel ve kimyasal özellikleri tanımlanmış olmalıdır (Altıntaş ve Kartal, 2021). Uçucu yağlardan istenilen etkinin gözlemlenebilmesi ve kullanım sonrası olası yan etkilerin önlenebilmesi için bu yağların, üretim aşamasından son kullanıcıya ulaşmasına kadar geçen tüm süreçte; kalite kontrol ve standardizasyon kurallarına eksiksiz bir şekilde uyulmuş olması, uçucu yağların kimyasal bileşim, saflık, kullanım yöntemini belirlenmesi ve depolama aşamasında ise hava geçirmez kaplarda ve ışık almayan ortamda muhafaza edilmesi gerekmektedir. (Altıntaş ve Kartal, 2021; Dunning, 2013).

Sonuç ve öneriler

Bu derleme ile, aromaterapinin; sporcularda stres yönetimi, yorgunluk hissiyatının geciktirilmesi, kilo kontrolü, ağrı hissiyatının yönetimi gibi sporcu performansının dolaylı yollardan arttırılması, çeşitli yaralanmaların tedavisinin desteklenmesi ve toparlanma süresinin hızlandırılması üzerindeki potansiyel etkileri kapsamlı bir şekilde ele alınmıştır. Sporcularda fiziksel performans kadar psikolojik dayanıklılığın da antrenman ve müsabaka başarısında kritik bir rol oynadığı bilinmektedir. Bu bağlamda, aromaterapi uygulamaları, sporcuların hem fiziksel hem de mental iyilik hallerini destekleyen tamamlayıcı bir yöntem olarak dikkat çekmektedir. Mevcut literatür, uçucu yağların sporcu sağlığı üzerindeki etkilerini giderek artan bir ilgi ile incelemekte ve çeşitli aromaterapi uygulamalarının farklı psikolojik ve fizyolojik parametreler üzerinde olumlu sonuçlar doğurabileceğini ortaya koymaktadır.

Bununla birlikte, aromaterapi uygulamalarının sporcularda etkin ve güvenli bir şekilde kullanılabilmesi için bazı önemli hususlara dikkat edilmelidir. Uçucu yağların kalitesi, doğru dozaj ve seyreltme oranları, doğru uygulama yöntemleri (inhalasyon, topikal, oral vb.) ve bireysel farklılıklar göz önünde bulundurulmalıdır. Ayrıca kullanılacak olan uçucu yağ; elde edilirken uluslararası standartlara uyulmuş olunmalı, üretim ve depolama esnasında herhangi bir kontaminasyona maruz kalmamış olmalı ve doğru koşullarda saklanmalıdır.

Uçucu yağların fototoksik ve alerjik reaksiyon riski taşıyabileceği ve bu yağların kullanımı esnasında dikkatli olunması gerektiği unutulmamalıdır. İlk kez kullanılacak olan uçucu yağ için yama testi yapılmalıdır. Uçucu yağların adölesan dönem, hamilelik dönemi gibi özel dönemlerde kullanımı dikkatle değerlendirilmeli; uçucu yağların olası toksik etkileri, ilaç etkileşimleri ve bireysel hassasiyetler göz önünde bulundurulmalıdır. Ayrıca uçucu yağ karışımları hazırlanırken birbirleriyle gösterebileceği sinerjik ya da antagonist etkiler dikkate alınmalı, güvenli ve etkili bir kullanım için uzman rehberliğinde hareket edilmelidir.

Bazı uçucu yağlar doping açısından risk oluşturabilmektedir. Bu nedenle ulusal ve uluslararası müsabakalara katılan sporcularda aromaterapi uygulamaları öncesinde kullanılacak yağların içeriği dikkatle incelenmeli ve Dünya Anti-Doping Ajansı (WADA) tarafından yayınlanan yasaklı maddeler listesi göz önünde bulundurulmalıdır.

Sonuç olarak, aromaterapi sporcu sağlığı ve performansına yönelik tamamlayıcı ve destekleyici bir yaklaşım olarak değerlendirilmektedir. Stres ve yorgunluk yönetimi, kilo kontrolü, ağrı hissiyatının azaltılması ve yara iyileşmesinin hızlandırılması gibi alanlarda umut verici sonuçlar sunmaktadır. Bu bağlamda aromaterapinin spor hekimliği, spor fizyoterapistliği, spor eczacılığı ve sporcu beslenmesi alanlarında multidisipliner bir yaklaşım ile ele alınması, sporcuların genel iyilik hali ve performansını maksimize etme potansiyelini arttıracaktır.

Yazar katkıları

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Hipnoterapi ve kadın sağlığı: Hipnoterapinin detaylarıyla bütüncül bir yaklaşım

Hypnotherapy and women's health: A holistic approach with the details of hypnotherapy

Fatma Bay*, Nisa Berfin Berk

KTO Karatay Üniversitesi, Sağlık Bilimleri Fakültesi, Ebelik Bölümü, Konya, Türkiye

ÖZET

Günümüzde tamamlayıcı bir tedavi yöntemi olarak kullanılan hipnoterapi, kişinin zihninin gevşeme ve dikkat halindeyken yeniden biçimlendirilmesine yardımcı olmaktadır. Hipnoterapi sayesinde kişinin olumsuz düşüncelerinin olumlu hale dönüşmesi amaçlanmaktadır. Hipnoterapinin ağrıyı yönetme, psikolojik sorunlar gibi çeşitli birçok alanda olduğu gibi kadın sağlığı üzerinde de faydalı olduğu görülmektedir. Bu makalede hipnoz ve hipnoterapi hakkında genel bilgiler verilerek, kulanım alanları ve özellikle kadın sağlığı ile etkisinin incelenmesi amaçlanmaktadır. Doğum öncesi dönem, doğum, emzirme, doğum sonu dönem ve kadın sağlığıyla ilgili sorunlar çalışmalarla birlikte incelendiğinde hipnoterapinin etkili olduğu görülmektedir. Çalışmalar incelendiğinde hipnoterapi, kadın sağlığını bütüncül bir yaklaşımla destekleyen tedavi yöntemleri arasında önemli bir yer tutmaktadır. Sağlık profesyonelleri olarak modern tıbbı tamamlayıcı tedavilerle destekleyerek bireyin sağlığını iyileştirme sürecinde önemli katkı sunabiliriz.

Anahtar kelimeler: Doğum, emzirme, hipnoterapi, hipnoz, kadın sağlığı

ABSTRACT

Hypnotherapy, which is used today as a complementary treatment method, helps reshape a person's mind while in a state of relaxation and focused attention. Hypnotherapy aims to transform an individual's negative thoughts into positive ones. It has been found to be beneficial in various areas, such as pain management and psychological issues, as well as in women's health. This article aims to provide general information about hypnosis and hypnotherapy, examine their areas of use, and specifically analyze their effects on women's health. When studies on the prenatal period, childbirth, breastfeeding, the postpartum period, and women's health-related issues are examined, hypnotherapy is shown to be effective. A review of the studies reveals that hypnotherapy holds a significant place among treatment methods that support women's health with a holistic approach. As healthcare professionals, we can make significant contributions to improving individual health by supporting modern medicine with complementary therapies.

Keywords: Childbirth, breastfeeding, hypnotherapy, hypnosis, women's health

***İletişim:**
fatma.bay@karatay.edu.tr

ORCID iD:
0000-0001-8840-1279

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Giriş

Hipnoz, kişinin farkındalığının, bulunduğu ortamın etki ve yansımalarından ayrılarak, daha çok içsel deneyimlere; yani duygu, düşünce ve hayal gücüne odaklandığı, özel bir bilinç hali olarak tanımlanmaktadır (Telli, 2020). Bu durumda kişi, hipnoterapistin veya hipnozu uygulayan kişinin telkin ve komutlarına açık hale gelmektedir. Hipnoz sırasında, bireyin bilinçaltına erişmek ve olumlu değişiklikler yapmak mümkün olmaktadır (Ceyhan ve Yiğit, 2013). Hipnoterapi, hipnozun bir terapi aracı olarak kullanıldığı, ruh sağlığı veya fiziksel sağlık sorunlarının tedavisinde faydalı olmayı amaçlayan bir yöntemdir (Haspolat ve Kavak, 2022). Hipnoterapi, farmakolojik olmayan bir müdahale olarak yan etkileri minimize eder ve uzun süreli davranışsal değişimlere olanak tanımaktadır (Kaçar, 2020). Her birey hipnoza aynı derecede duyarlı değildir; bu durum, beyindeki yapısal ve fonksiyonel farklılıklara bağlı olarak değişmektedir (Hoeft vd., 2012). Hipnoterapi derin gevşeme ve sakinlikle rahatlamaya ulaşmak için hipnoterapi uzmanı eşliğinde ve gözetiminde yapılan (Indriyani ve Asmuji, 2014) ve günümüzde giderek yaygınlaşan tamamlayıcı ve alternatif tedavi yöntemlerinden biridir (Taştan vd., 2015).

Deneysel araştırmalar hipnozun ağrı, kemoterapiyle ilişkili mide bulantısı ve kusma, psikosomatik bozukluklar, sigarayı bırakma, obezite ve depresyon gibi çeşitli sorunlar ve semptomlar üzerinde oldukça etkili bir müdahale olduğunu ortaya koymuştur. Aynı zamanda hipnozun anksiyete için de oldukça etkili bir müdahale olduğu bilinmektedir (Hauser vd., 2016). Hipnozun psikolojik rahatsızlıklar, ağrı yönetimi, bağımlılıklar, kadın sağlığı gibi geniş bir yelpazede kullanım alanı bulunmaktadır. Hipnozun gebelik, doğum ve doğum sonu dönemde fiziksel ve psikolojik sorunlar yaşayan kadınlar için faydalı olduğu çalışmalarda da görülmektedir (Dini vd., 2017).

Kadın yaşam dönemleri boyunca (çocukluk, puberte, cinsel olgunluk, klimakterium ve yaşlılık) yaşadığı menstural siklus, gebelik, emzirme veya menopoz gibi süreçlerde ağrı, kusma, bulantı, sıcak basmaları gibi semptomları sıklıkla yaşayabilmektedir. Yaşanan bu semptomlara yönelik konforu ve yaşam kalitelerini artırmak, semptomları azaltmak ve önlemek, daha sağlıklı olmak ve sağlık davranışları göstermek amacıyla kadınlar tamamlayıcı ve alternatif tedavi yöntemleri kullanabilmektedir (Öztürk Özen ve Demirci, 2023). Türkiye'de genel popülasyonda tamamlayıcı ve alternatif tedavi uygulamalarının kullanım sıklığı ve yöntemlere göre dağılım oranı tam olarak bilinmemekle birlikte (Şahin, 2017) yakın zamanda yapılan bir çalışmada hipnoz veya hipnoterapi kadınlar arasında tercih edilen bir tedavi yöntemi olmamıştır (Öztürk Özen ve Demirci, 2023). Bu nedenle, hipnoz ve hipnoterapinin kadın üreme sağlığı sorunlarına çözüm sunup sunamayacağına dair literatürde sınırlı da olsa bazı bilgiler bulunmaktadır. Çalışmada; hipnoz ve hipnoterapinin tarihçesi, etki mekanizması, kullanım alanları ve kadının gelişim dönemleri içindeki karşılaşabileceği üreme sağlığı problemlerine dair hipnoterapiyi ele alan çalışmalara odaklanılması amaçlanmıştır.

Dünya'da hipnoz ve hipnoterapinin tarihçesi

Hipnozun tarihi, Yunan ve Antik Mısır uygarlıklarına dayanmaktadır. Bu dönemde insanların, çeşitli dini inanışlar ve şifacılık uygulamaları sırasında hipnotik bir odaklanma haline geçtiği bilinmektedir (Borbély ve Çeşmeli, 2022). Modern hipnozun temelleri ise, 18. yüzyılda Franz Anton Mesmer tarafından atılmıştır. Mesmer, "hayvan manyetizması" adını verdiği bir enerji alanının, hastalıkların tedavisinde kullanılabileceğini ortaya atmıştır (Gündüz, 2021). Mesmer'in teorileri bilimsel temele dayanmasa da hipnozun gelişiminde önemli bir kaynak olmaktadır (Öztürk, 2020). 19. yüzyılda, İngiliz bir cerrah olan James Braid hipnozu bilimsel olarak incelemeye başlamış ve "hipnoz" terimini ortaya atmıştır (Özakkaş, 2007). Braid, hipnozu, "fiziksel ve zihinsel durumlar arasında bir köprü'' olarak tanımlamış ve bu teknikle bazı hastalıkları tedavi etmeyi başarmıştır. Hipnozun modern psikolojinin içine girmesi ise 20. yüzyılda, Sigmund Freud gibi önemli isimler sayesinde olmuştur. Freud, hipnozu psikoterapinin bir aracı olarak kullanmış ve bilinçaltına erişim sağlamak için hipnozu kullanmıştır (Kılıç, 2023). Araştırmacı psikolog olan Clark Hull, 1933 yılında, hipnoz olgusu hakkında kontrollü çalışmaların bildirildiği ilk kitabını yayımlamıştır. Hull, modern deneysel bilim ile bilinmeyen bir çalışma alanı olan hipnozu detaylıca açıklayan ilk kişi olmuştur. Bilimsel referansları kusursuz olduğundan, Hull'un öncü çalışmaları, akademik önyargıyı büyük ölçüde kırmıştır ve Hull 1936'da Amerikan Psikoloji Derneği'nin başkanlığını yapmıştır (Özakkaş vd., 2020). Milton H. Erickson tarafından 1930'lu yıllarda yazılan makaleler, doktorları ve psikoterapistleri hipnoz ile ilgili düşünmeye ve araştırmaya teşvik etmiştir. Aynı zamanda Erickson, Amerikan Klinik Hipnoz Topluluğu'nun ilk başkanı ve Amerikan Klinik Hipnoz Dergisi'nin editörü olarak dünya çapında tanınmıştır (Tatar, 2022). Birinci dünya savaşında Almanya'da Simmel, İngiltere'de ise Hadfield savaşın etkilerini tedavi etmek için hipnozu kullanmışlardır. Hadfield, hipnozu psikoanalitik yöntemlerle bütünleştiren ve "hipnoanaliz" terimini kullanan ilk kişidir (Özakkaş vd., 2020). İngiliz Tıp Cemiyeti'nin görevlendirdiği bir grup 1953'te, hem fiziksel hem de psikolojik rahatsızlıklarda, hipnozun kullanımını resmen onaylamıştır ancak Amerikan Tıp Cemiyeti bu onayı üç yıl sonra vermiştir (Maviş, 2022). Bu gelişmeler ışığında

hipnoz, tıp mesleği ve akademik çevrelerde önyargıları büyük ölçüde giderebilmiş, meşru bir bilim alanı ve tedavi yöntemi olarak hak ettiği yerini almıştır (Talhaoğlu, 2021).

Türkiye'de hipnoz ve hipnoterapinin tarihçesi

Ülkemizde hipnoza ilişkin görüşler, 1935 yılında bir felsefeci olan Cemil Sena Ongun'un, Pierre Janet'in "Hipnotizma" ve "Ruhi Mucizeler" adlı kitaplarının çevirisini gerçekleştirmesi ile başlamıştır (Özakkaş vd., 2020). 1950'lerde Dr. Bedri Ruhselman hipnozu ispritizma çalışmalarında kullanmış, 1951 yılında hipnotizör D. Watson, İstanbul ve Ankara'daki tıbbi uygulamalarıyla dikkat çekmiştir. 1951-1979 yılları arasında Dr. Hüsnü İsmet Öztürk "Bilinçli Hipnoz" yöntemini kullanarak 2000 hastayı hipnotize etmiştir ve hipnoz tekniği ile 250'den fazla hastada yalnızca hipnoanestezi kullanarak cerrahi operasyonlar gerçekleştirmiştir (Telli, 2020). 1960'ta Prof. Dr. Recep Doksat uzmanlık tezini hipnoz üzerine yazmış, ardından bilimsel kitaplar yayınlamıştır (Akalın vd., 2023). 1970'lerde hipnoz diş hekimliği ve pediatri alanlarında kullanılmaya başlanmıştır (Gündüz, 2021). 1991'de Tıbbi Hipnoz Derneği kurulmuş ve 2000'lerde Yeditepe Üniversitesi ile yürütülen eğitim programları başlamıştır (Özakkaş vd., 2020). Türkiye Psikiyatri Derneği, 2006'da Dr. Şeref Özer koordinatörlüğünde "Hipnoz ve Hipnoterapi Bilimsel Çalışma Birimi"ni kurmuştur. Sağlık Bakanlığı, 2014'te hipnoz uygulamasına yönelik sertifikalı eğitim programını yürürlüğe koymuş, günümüzde hipnoz eğitimi birçok üniversitede verilmeye başlanmıştır. Dr. Tahir Özakkaş, hipnozun bilimsel temellerde yaygınlaşmasında önemli katkılarda bulunmuştur. Eserleri ve eğitimleriyle alanın gelişimine öncülük etmiştir (Özakkaş vd., 2020).

Hipnoz ve hipnoterapinin etki mekanizması

Hipnozun etkileri, nörolojik ve psikolojik mekanizmalara dayanır (Potié vd., 2016). Hipnoz sırasında beyinde özellikle dorsolateral prefrontal korteks (yönetici kontrol) ile dorsal anterior singulat korteks (dikkat odaklanması) arasındaki bağlantının güçlendiği gösterilmiştir. Bu durum, kişinin odaklanmasını artırırken dış etkenlerin dikkat dağıtıcı etkisini azaltarak bireyin telkinlere açık hale gelmesine yol açmaktadır. Böylece bireyin günlük kaygılarından uzaklaşmasını ve terapiye daha açık hale gelmesini sağlamaktadır (De Pascalis, 2024). Sonuçta kişinin algısı, duyguları ve davranışlarını değiştirmek mümkündür (Çelik, 2017). Hipnoterapide, bu durum terapötik hedefler doğrultusunda yönlendirilmektedir (Ruysschaert, 2014) ve kişinin davranışsal, duygusal veya bilişsel süreçlerini değiştirmeye yönelik bir araç olarak kullanılmaktadır (Piştof ve Şanlı, 2013).

Beyinde hipnoz sırasında meydana gelen süreçler bulunmaktadır. Beyin dalgaları, hipnoz sırasında alfa ve teta seviyelerine geçer, bu sayede hipnoz uygulanan kişinin daha rahat ve odaklanmış bir hale gelmesi sağlanmaktadır. Plastisite, beynin nöroplastisite özelliklerini tetikleyerek yeni bağlantılar oluşmasını kolaylaştırır. Bu da davranış değişikliğini destekler. Kortikal aktivite, hipnoz sırasında prefrontal korteksin aktivitesi azalır ve birey, telkinlere daha açık hale gelmektedir (Salon, 2022). Hipnoterapi, beyin işleyişini ve nörolojik yolları etkileyerek çalışır. Hipnoz sırasında beynin belirli bölgelerinde aktivite değişiklikleri gözlemlenmektedir (Tarlacı, 2023). Beynin anterior singulat korteks, insula ve prefrontal korteks gibi bölgelerinde yapılan nörogörüntüleme çalışmaları, hipnoz sırasında bu alanlarda artan aktivite olduğunu göstermiştir. Bu durum, bireyin ağrı gibi duyusal uyaranlara olan duyarlılığının azalmasına neden olabilmektedir (Landry vd., 2017).

Hipnoterapinin kullanım alanları

Hipnoterapi, geçmişten günümüze kadar psikoterapi alanında önemli bir yer edinmiş ve günümüzde halen çeşitli fiziksel, zihinsel ve duygusal rahatsızlıkların tedavisinde kullanılmaktadır (Işıkay, 2019). Hipnoterapinin kullanıldığı tedavi alanları aşağıda belirtilmiştir:

Psikolojik rahatsızlıkların tedavisi

Hipnoterapi, özellikle kaygı bozuklukları, depresyon ve travma sonrası stres bozukluğu (TSSB) gibi rahatsızlıkların tedavisinde etkili bir yöntemdir. Hipnoterapinin bireyin stres düzeyini azaltmada ve rahatlama sağlamada etkili olduğu gösterilmektedir (Bulut vd., 2022). TSSB, bireyin travmatik bir olay sonrası tekrar eden anılar, kabuslar ve yüksek stres düzeyi ile baş etmede zorlandığı bir rahatsızlıktır (Trajkov, 2023). Travma terapilerinde hipnoterapinin, bireylerin travmayı yeniden anlamlandırmasına ve duygusal yükü hafifletmesine olanak sağladığı görülmektedir. Özellikle askerler, kazazedeler ve cinsel istismar mağdurlarında etkili olduğu belirtilmektedir (Lynn vd., 2012).

Kaygı bozuklukları, bireylerin günlük yaşamlarını olumsuz etkileyen yaygın bir psikolojik sorundur (Panayiotou ve Karekla, 2013). Hipnoterapi, kaygı bozukluklarının tedavisinde özellikle derin gevşeme sağlama ve zihinsel telkinlerle kaygıyı azaltma amacıyla kullanılmaktadır (Telli, 2020). Kaygı bozukluğu olan bireylerde telkinler, derin nefes alma teknikleri ve gevşeme hipnozu ile stres yönetimi sağlanabilmektedir (Sarman, 2024). Özellikle sosyal kaygı ve genel kaygı bozukluklarında etkili olduğu görülmektedir (Noyan ve Sertel-Berk, 2007).

Depresyon, bireyin kendine olan güvenini kaybetmesi ve umutsuzluk hissetmesi ile karakterize bir durumdur. Hipnoterapi, bireyin olumsuz düşünce kalıplarını

değiştirmesine ve pozitif duygular geliştirmesine yardımcı olmaktadır (Bulut vd., 2022). Depresyon tedavisinde hipnoterapinin bireyin kendine yönelik olumsuz düşüncelerini pozitif düşüncelerle değiştirdiği ve enerji seviyelerini artırdığı gösterilmektedir (Alladin ve Alibhai, 2007).

Obsesif Kompulsif Bozukluk (OKB), bireyin kontrol edemediği takıntılı düşünceler ve tekrarlayan davranışlarla kendini göstermektedir. Hipnoterapi, bireyin bu döngüleri kırmasına ve zihinsel olarak rahatlamasına destek sağlamaktadır (Ayaslı vd., 2020). Hipnoterapi, OKB hastalarının obsesyon, kompulsiyonlarını yönetmesine ve bu davranışları azaltmasına yardımcı olabilmektedir (Gruzelier, 2002).

Korku ve fobiler, bireylerin günlük yaşamlarını olumsuz etkileyebilmektedir. Fobiler, bireyin belirli bir olay veya varlığa karşı aşırı korku duymasına neden olan bir anksiyete bozukluğudur. Hipnoterapi, fobilerle başa çıkmada ve bireyin korkularını yeniden yapılandırmasında önemli bir araç olmaktadır (Gürsoy, 2020).

Hipnoterapi, psikolojik rahatsızlıkların tedavisinde etkili ve destekleyici bir terapi yöntemi olarak öne çıkmaktadır (Öztürk vd., 2020). Psikoloji ile ilgili farklı rahatsızlıkların tedavisinde de hipnoterapinin olumlu etkileri çalışmalarda gösterilmektedir (Abramowitz vd., 2008; Alladin ve Alibhai, 2007; Kirsch ve Montgomery, 2022; Gruzelier, 2002). Ayrıca, daha geniş çaplı klinik araştırmalar, hipnoterapinin uzun vadeli etkilerini anlamamıza katkı sağlayacaktır (Haspolat ve Kavak, 2022).

Ağrı yönetimi

Hipnoterapi, kronik ağrı yönetiminde sıkça başvurulan bir tekniktir (Aydın ve Çilingir, 2020). Özellikle migren, fibromiyalji ve kanser hastalarında ağrıyı hafifletmek, ağrı algısını değiştirmek, stres düzeylerini azaltmak ve bireyin rahatlamasını sağlamak amacıyla kullanılmaktadır (Tuna, 2023). Hipnoterapi, bireyin ağrıyı farklı bir şekilde algılamasını sağlayarak yaşam kalitesini artırmaktadır (Jensen vd., 2015).

Kronik ağrı, bireyin hayat kalitesini önemli ölçüde düşüren geniş zaman aralığında devam eden bir rahatsızlıktır (Bozhüyük vd., 2012). Hipnoterapi, bu tür ağrılarda beynin ağrıyı algılama şeklini değiştirmek ve bireyin ağrı ile başa çıkma becerilerini artırmak için kullanılabilmektedir (Hillgard ve Hillgard, 2013). Aynı zamanda hipnoterapi, kronik bel ağrısı, artrit ve nöropatik ağrı gibi durumların yönetiminde etkili bir destekleyici tedavi yöntemi olarak da tercih edilebilmektedir (McKittrick vd., 2022). Ağrı algısını azaltmak ve iyileşme sürecini hızlandırmak için de ameliyat öncesi ve sonrası dönemde hipnoterapi uygulanabilmektedir (Chester vd., 2016).

Kanser hastalarında ağrı hem fiziksel hem de duygusal yük oluşturmaktadır (Girgis vd., 2013). Hipnoterapi, ağrı algısını değiştirmenin yanı sıra stres ve kaygıyı azaltarak bu süreçte destekleyici bir rol oynamaktadır (Frisaldi vd., 2015). Kanser hastalarında ağrı ve stres yönetiminde hipnoterapi, yaşam kalitesini artırmak için de kullanılabilmektedir (Elkins vd., 2004).

Fibromiyalji, yaygın kas, iskelet ve eklem ağrıları, yorgunluk ve uyku bozuklukları ile betimlenen kronik bir durumdur (Koca, 2015). Hipnoterapi, fibromiyalji semptomlarını hafifletmek ve fibromiyalji hastalarında ağrı algısını değiştirme ve gevşeme sağlamada etkili bir tedavi seçeneğidir (Castel vd., 2007).

Migren, şiddetli baş ağrılarıyla kendini gösteren nörolojik bir rahatsızlıktır (Sağlı Diren, 2020). Hipnoterapi, migren ataklarının sıklığını ve şiddetini azaltmak için uygulanabilmektedir (Flynn vd., 2019). Telkinler ve gevşeme teknikleri, bu süreçte bireyin stres seviyesini azaltarak etkili bir sonuç sağlamaktadır (Hammond, 2007).

Kadın sağlığı ve hipnoterapi

Kadın sağlığı, üreme sistemiyle ilgili sorunlardan doğum sürecine, menopozdan ruhsal sağlık problemlerine kadar geniş bir yelpazede ele alınması gereken bir alandır (Keten ve Edis, 2021). Son yıllarda, bu kapsamda alternatif terapiler arasında hipnoterapi dikkat çekmektedir (Aslan, 2016). Hipnoterapi, kadınların yaşamlarında karşılaştığı çeşitli zorluklara yönelik güvenilir ve etkili bir yöntem olarak karşımıza çıkmaktadır (Beebe, 2014). Özellikle doğum sırasında ağrıyı azaltmak, doğum korkusunu gidermek, travma sonrası stres bozukluğunu tedavi etmek ve yaşam kalitesini artırmak amacıyla kullanılmaktadır (Amanak vd., 2013).

Gebelik ve hipnoterapi

Gebelikte; hafif düzeyde ağrı, yorgunluk, uyku problemleri, bulantı, kusma, anksiyete, gibi yaygın olarak görülen sorunlar genellikle tedavi gerektirmeyen, risksiz ve basit rahatsızlıklar olarak değerlendirilmektedir (Şen vd., 2020). Basit gibi görünse de bu problemler, kadının fiziksel sağlığını ve hayat kalitesini negatif yönde değiştirmektedir (Koyun vd., 2011). Gebelikteki bu tarz sorunlar için geleneksel tamamlayıcı tıp uygulamaları kullanılabilmektedir (Sülü vd., 2022). Hipnoterapi de bunlardan biridir. Hipnoterapi, özellikle gebeliğin ilk trimesterında bulantı kusma şikayetleri için sık kullanılan nonfarmakolojik bir yöntemdir (Şen vd., 2020). Yapılan çalışmalarda hipnozun, bulantı ve kusma şikayetlerini iyileştirdiği ve stres ve kaygıyı azalttığı sonuçlarına ulaşılmıştır (Catsaros ve Wendland, 2023).

Doğum sürecinde hipnoterapi: Hipnodoğum yaklaşımı

Hipnodoğum (hypnobirthing), hipnoterapinin doğum sürecinde kullanılan en bilinen uygulamalarından biridir. Bu yaklaşım, doğum sırasında annenin zihinsel ve fiziksel olarak rahatlamasına yardımcı olarak ağrıyı azaltmayı, doğum deneyimini pozitif ve mutlulukla hatırlamak isteyeceği bir anı haline getirmeyi hedeflemektedir (Buckley, 2013). Hipnodoğum yönteminin annenin stres düzeylerini azaltarak doğum süresini kısalttığı ve doğumun daha az müdahale ile tamamlanmasını sağladığı belirtilmektedir. Ayrıca, hipnoterapinin rahim kaslarının uyum içinde çalışmasına yardımcı olduğu, annenin doğum korkularını azalttığı ve doğum süresini kısalttığı çalışmalarda gösterilmektedir (Syswianti ve Wahyuni, 2023; Rosalina vd., 2024). Hipnoterapinin korku, ağrı ve doğum deneyimi üzerine etkisinin incelendiği ve 82 çalışmanın dahil edildiği sistematik derlemede; hipnoterapinin doğum sırasında korku ve ağrıyı azaltması yanı sıra genel doğum deneyiminde bir iyileştirmeye yol açtığı bildirilmektedir (Fernández-Gamero vd., 2024).

Doğum sonrası depresyon ve stres yönetimi

Doğum sonu, anneliğe yeni adım atmış kadınlar ve çevrelerindeki insanlar için önemli bir dönemdir (Koç ve Öztoprak, 2023). Aynı zamanda büyük ölçüde mutluluk, heyecan gibi pozitif duyguların yaşandığı, aile içindeki bağlarının güçlendiği bir dönem olabildiği gibi anneliğe ve bebeğe uyum sağlamakta zorlanılan bir süreç de olabilmektedir (Cin ve Bingol, 2024). Doğumdan sonra kadınlar fiziksel ve psikososyal durumlarında çeşitli değişiklikler yaşamaktadırlar (Arslantaş vd., 2020). Annenin postpartum dönemde yaşadığı değişimlerle baş edemediği, yeterli destek görmediği durumda stres seviyesinin artması postpartum depresyon ve stres yaşamasına neden olmaktadır (Aydın vd., 2022). Doğum sonrası depresyon (postpartum depresyon), birçok annenin doğumdan sonraki ilk aylarında yaşadığı ciddi bir ruhsal sağlık sorunudur (Beji vd., 2022). Hipnoterapi, bu depresyonun belirtilerini hafifletmek ve annenin kendine olan güvenini artırmak, özgüven kazandırmak için etkili bir yöntem olarak kullanılmaktadır. Ayrıca, hipnoterapinin doğum sonrası uyku düzenini iyileştirdiği ve stres seviyelerini azalttığı düşünülmektedir (Anık Çankaya, 2023). Literatür incelendiğinde, gebelikleri boyunca hipnoz müdahalesi yapılan 28 kadının kontrol grubuna göre daha düşük anksiyete, depresif semptomlar ve postpartum depresyon yaşadığı bildirilmektedir (Beevi vd., 2019).

Emzirme ve hipnoterapi (Hipnoemzirme)

Emzirme sürecinde hipnoz ile anne üzerinde olumlu düşünce ve telkinlerle anneyi sakinleştirmek amaçlanmaktadır (Kılcı ve Sevil, 2021). Hipnoterapinin endorfin ve prolaktin hormonlarının salınımını desteklediği, doğumdan sonraki ilk günlerde kolostrum salınımında etkili olduğu görülmektedir (Kusmiyati ve Wahyuningsih, 2014). Hipnoemzirme, doğumdan sonra annede var olan enerjiyi koruyarak ve dönüştürerek, emzirme sürecinin güvenli, huzurlu ve sorunsuz gerçekleşmesini hedefleyen doğal bir yaklaşımdır. Bu yöntem, annelerin gevşemesini, sakinliğini korumasını, stresinin azaltmasını, nefes alışverişini yavaşlatmasını sağlayan bir yöntemdir (Demirbağ ve Tokat, 2023). Masruroh ve Andriani (2018), primipar emziren annelerde, hipnoemzirmenin kolostrum salınımı üzerindeki etkisini incelemiş, bu yöntemin kolostrum miktarı üzerinde istatistiksel bir fark yaratmadığını fakat kolostrum salınımını hızlandırdığını ortaya koymuştur (Masruroh ve Andriani, 2018). Emzirme hipnozu, oksitosin hormonunun salınımını uyarmak için olumlu telkinler programlanmasıdır. Anne sütünü artırmak için emzirme hipnozunun kullanıldığı yarı deneysel bir çalışmada kontrol grubuna göre anne sütü salınımını artırdığı tespit edilmiştir (Widayanti vd., 2022).

Dismenore ve hipnoterapi

Dismenore, alt karın bölgesinde kramp tarzında, bazen sırta doğru yayılan ağrılar ile baş ağrısı, mide bulantısı, yorgunluk, kusma, sinirlilik, ishal ve genel bir rahatsızlık hissinin yaşanabildiği regl dönemi rahatsızlığıdır. Yapılan çalışmalarda dismenore yaşayan gençlerin rahatsızlık nedeniyle sıklıkla işe veya okula gidemediğini, bunun da önemli bir sosyal ve ekonomik etkiye sahip olabileceğini göstermektedir (Fernández-Martínez vd., 2019). Hipnoterapi, bu tür ağrıları yönetmek için alternatif bir çözüm sunmaktadır. Literatür incelendiğinde yapılan bir çalışmada hipnozun dismenoreye bağlı ağrının yoğunluğunu ve süresini azalttığı bildirilmektedir (Shah vd., 2014).

Menopoz sürecinde hipnoterapi

Menopoz, kadınların hormonal dengelerinde ciddi değişimlerin yaşandığı ve birçok fiziksel ile duygusal semptomun ortaya çıktığı, kadınları fiziksel, duygusal ve sosyal açıdan etkileyen bir dönemdir (Vardar vd., 2020). Hipnoterapi, sıcak basmaları, uyku problemleri ve anksiyete gibi menopoz semptomlarını hafifletmek amacıyla kullanılmaktadır (Yetişmiş vd., 2023). Ayrıca, hipnoterapi sırasında kullanılan telkinler ve gevşeme teknikleri, menopoz dönemindeki ruhsal dalgalanmaları düzenleyerek kadının kendini daha dengeli hissetmesini sağlamaktadır (Kaba ve Bozkurt, 2020). Sıcak basmaları yaşayan kadınlara ses kayıtları ile hipnoterapi uygulanan retrospektif bir çalışmada, hipnoterapinin sıcak basmaları için etkili bir müdahale olduğu, hormonal veya farmakolojik müdahale olmadan sıcak basmalarını azaltarak kadınların hayatlarını iyileştirme potansiyeline sahip olduğu bildirilmiştir. Aynı zamanda mobil uygulama ile

hipnoterapiye erişilebilirliğinde artırılabilmesi umut verici bir sonuç olarak dikkat çekmektedir (Scheffrahn vd., 2025).

İnfertilite tedavisi ve hipnoterapi

Biyolojik, psikolojik, sosyal ve kültürel olarak çoğu yönden önemli sorunlar yaratan infertilite (Yanıkkerem, 2008), üreme çağındaki çiftlerin bir yıl boyunca, herhangi bir aile planlaması yöntemi kullanmaksızın cinsel ilişkiye rağmen gebe kalamamasıdır (Gure, 2023). İnfertilite tedavisi gören kadınlar, sıklıkla yüksek seviyede stres ve kaygı yaşamaktadır (Keskin ve Gümüş, 2014). Hipnoterapi, bu sürecin daha az stresli bir şekilde yönetilmesine yardımcı olmaktadır (Amanak vd., 2013). Domar ve arkadaşları (2000), hipnoterapinin infertilite tedavisi sırasında stres yönetiminde etkili olduğunu ve tedaviye uyumu artırdığını ifade etmiştir (Domar vd., 2000). Levitas ve arkadaşları (2006), hipnoterapi uygulanan hastaların gebe kalma ve implantasyon oranlarında artma olduğunu ortaya koymuştur (Levitas vd., 2006).

Cinsel sağlık ve hipnoterapi

Kadınların cinsel sağlık sorunları, genellikle psikolojik faktörlerle bağlantılıdır (Arcos vd., 2023). Hipnoterapi, vajinismus, cinsel isteksizlik ve anorgazmi gibi durumların tedavisinde etkili bir yöntemdir (Kahıloğulları ve Karaaziz, 2024). Yapko (2012), hipnoterapinin cinsel sağlık sorunlarının kökenindeki bilinçaltı korkuları ve travmaları çözümlemeye yardımcı olduğunu belirtmiştir (Yapko, 2012). Özellikle vajinismus tedavisinde hipnoterapi, pelvik kasların gevşemesini ve bireyin kendini güvende hissetmesini sağlamaktadır (Haspolat ve Kavak, 2022).

Sonuç

Hipnoterapi, tarih boyunca mistik bir olgu olarak görülmüş, ancak modern bilimle birlikte etkili bir terapi yöntemi olarak kabul edilmiştir (Ceyhan ve Yiğit, 2016). Bu yöntem, kişinin olumsuz düşünce, duygu ve davranışlarını olumlu hale dönüştürmeyi amaçlamaktadır. Günümüzde pek çok rahatsızlığın giderilmesinde tamamlayıcı veya alternatif bir tedavi olarak kullanılan hipnoterapi, özellikle kadın sağlığı alanındaki olumlu etkileriyle dikkat çekmektedir. Kadınların yaşamları boyunca karşılaşabileceği üreme sağlığı problemlerine yan etkisiz bir çözüm sunduğu görülmektedir. Bu yönüyle hipnoz ve hipnoterapi, kadın sağlığını bütüncül bir yaklaşımla destekleyen önemli tamamlayıcı ve alternatif tedavi yöntemlerinden biri olarak öne çıkmaktadır. Ayrıca, hipnoterapiye erişimi kolaylaştıracak teknolojik gelişmelerin hayata geçirilmesi ve yaygınlaştırılması gerekmektedir. Ancak, hipnoterapinin etkinliği ve güvenliği konusunda daha fazla bilimsel araştırmaya ihtiyaç duyulmaktadır. Özellikle, kadın sağlığı alanındaki kullanımını destekleyen randomize kontrollü çalışmalar, bu yöntemin sağlık sistemine entegrasyonu için güçlü bir temel oluşturabilir. Hipnoterapinin, modern tıp ve diğer tamamlayıcı tedavilerle bütüncül bir yaklaşımla entegre edilmesi, bireylerin sağlık ve iyilik halini destekleme sürecinde önemli bir katkı sağlayabilir.

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Fikir/Konsept: Fatma Bay, Nisa Berfin Berk; Tasarım: Fatma Bay, Nisa Berfin Berk; Kontrol/Denetim: Fatma Bay, Nisa Berfin Berk; Veri Toplanması ve/veya İşleme: Fatma Bay, Nisa Berfin Berk; Analiz ve/veya Yorum: Fatma Bay, Nisa Berfin Berk; Literatür Taraması: Fatma Bay, Nisa Berfin Berk; Makaleyi Yazan: Fatma Bay, Nisa Berfin Berk; Eleştirel İnceleme: Fatma Bay, Nisa Berfin Berk; Referanslar ve Finansman: Fatma Bay, Nisa Berfin Berk; Malzemeler: Fatma Bay, Nisa Berfin Berk.

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