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Ultrasound Assisted Extraction of Phenolic and Flavonoid Compounds from *Anthemis cotula*: Antioxidant Potential Assessment

Fatma Özlem Kargın Solmaz[1*], Cengiz Sarıkürkcü[1]

[1]Afyonkarahisar Health Sciences University, Faculty of Pharmacy, 03030, Afyonkarahisar,Türkiye
* ozlem.solmaz@afsu.edu.tr
*Orcid No: 0000-0002-3908-3371

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Abstract

The exploration of effective extraction methods and bioactive potential in medicinal plants remains a critical focus for natural product research. This study aimed to evaluate the chemical composition and antioxidant properties of methanol and water extracts obtained from *Anthemis cotula* L. using ultrasound-assisted extraction. The extracts were characterized for extraction yield, total phenolic content (TPC), total flavonoid content (TFC), and antioxidant activities via six assays: CUPRAC, FRAP, phosphomolybdenum, DPPH, ABTS, and ferrous ion chelating activity. The water extract exhibited a higher yield (19.99%) compared to the methanol extract (11.43%). However, the methanol extract demonstrated superior TPC and TFC, with values of 64.33 mg GAEs/g extract and 39.22 mg REs/g extract, respectively, compared to 56.27 mg GAEs/g extract and 27.98 mg REs/g extract for the water extract ($p < 0.05$). Antioxidant assays revealed that the methanol extract possessed stronger reducing power, with CUPRAC and FRAP values of 262.83 and 154.98 mg TEs/g extract, respectively, compared to 235.98 and 127.53 mg TEs/g extract for the water extract. DPPH and ABTS radical scavenging activities were comparable between extracts, with IC_{50} values indicating similar efficacy. Notably, the water extract excelled in ferrous ion chelating activity (12.30 mg EDTAEs/g extract, IC_{50} = 1.06 mg/mL), outperforming the methanol extract (8.55 mg EDTAEs/g extract, IC_{50} = 1.53 mg/mL). These findings underscore the potential of A. cotula extracts, particularly in chelating metal ions and exhibiting reducing power. Future studies may focus on isolating bioactive compounds responsible for these activities and exploring their applications in pharmaceutical or nutraceutical formulations.

Keywords: *Anthemis cotula*, ultrasound assisted extraction, phenolic compounds, antioxidant activity.

1. Introduction

Plants serve as an abundant reservoir of secondary metabolites, many of which exhibit medicinal and aromatic properties. It is estimated that approximately 100,000 secondary metabolites have been identified across 50,000 plant species, with an additional 4,000 new compounds being discovered annually from various plants [1,2]. These natural products have been integral to human healthcare for millennia, finding applications as drugs, antioxidants, flavors, fragrances, dyes, insecticides, and pheromones. However, the widespread adoption of synthetic pharmaceuticals in the 20th century led to a decline in the reliance on plant-based medicines, with many believing that synthetic alternatives would ultimately replace traditional herbal remedies [3].

In recent decades, there has been a renewed interest in herbal medicines, largely due to the growing recognition of the adverse effects associated with synthetic drugs and the perception that plant-derived remedies are safer with fewer side effects. As a result, the global herbal medicine market, currently valued at approximately $62 billion, is projected to expand significantly, potentially reaching $5 trillion by 2050. The annual growth rate of the herbal medicine industry, encompassing both herbal products and raw materials, ranges from 5% to 15%, suggesting an increasing demand for plant-derived pharmaceuticals in the near future [3,4].

Despite this promising growth, the large-scale utilization of medicinal plants in healthcare is hindered by several challenges. These include the low concentration of active compounds in specific plant tissues, the low priority given to medicinal crops, technical challenges in cultivation, overexploitation of wild medicinal plants,

unsustainable harvesting practices, and the conversion of natural habitats to agricultural lands [3].

The genus *Anthemis* (also known as Matricaria) includes approximately 210 species distributed across regions such as the Mediterranean, Europe, Southwest Asia, and South Africa. Many species within this genus have been utilized in traditional medicine since the Roman era [5]. For example, *A. nobilis* has been traditionally employed as a diaphoretic, emetic, antispasmodic, sedative, carminative, and for alleviating intestinal cramps [6]. The flowers and aerial parts of *A. cretica* have been used to address stomach pain and kidney stones [7]. Infusions of *A. aciphylla* have been consumed to relieve intestinal and abdominal colic, while decoctions have been applied to treat sunburns and skin inflammation [8]. Similarly, *A. cotula* has been used in the treatment of conditions such as psoriasis, fever, gastrointestinal disorders, dysentery, and gouty arthritis. For psoriasis, a paste made by mixing 50 mL of powdered *A. cotula* flowers with 15 mL of olive oil is applied 3 to 5 times daily. Additionally, the juice of *A. cotula* has been employed as a natural insect repellent [9,10].

This study focuses on exploring the bioactive potential of *A. cotula*, a plant known for its traditional medicinal applications and phytochemical richness. By utilizing ultrasound-assisted extraction (UAE) with methanol and water as solvents, the research aims to quantify the total phenolic and flavonoid contents of the resulting extracts. Furthermore, the antioxidant activities of these extracts will be evaluated to provide insights into their potential applications as natural antioxidant sources. This investigation seeks to contribute to the existing body of knowledge on *A. cotula* by shedding light on its phytochemical composition and bioactivity through modern extraction and analytical techniques.

2. Materials and Methods

2.1. Plant material and extraction procedure

The aerial parts of *A. cotula* (elevation: 720 m, coordinates: 37°30'83"N, 28°17'32"E; Herbarium number: O.1408) were gathered on April 22, 2023, from Güre village in Kavaklıdere-Muğla, Türkiye. The plant material was identified by Dr. Olcay Ceylan, and a voucher specimen was deposited in the Herbarium of the Department of Biology at Muğla Sıtkı Koçman University. The collected samples were air-dried in the shade for several weeks and then ground into a fine powder using a laboratory mill.

Ultrasound-assisted extraction (UAE) was carried out for one hour in a sonication bath, using methanol and water as solvents at a sample-to-solvent ratio of 1:20. After extraction, the aqueous extract was freeze-dried, while the methanolic extract was concentrated under reduced pressure using a rotary evaporator. Both extracts were stored at 4°C for subsequent analysis.

2.2. Quantification of total phenolics and flavonoids

The aluminum chloride colorimetric method was employed to determine the total flavonoid content (TFC), while the total phenolic content (TPC) was assessed using the Folin-Ciocalteu reagent. The results were expressed as rutin equivalents (REs) and gallic acid equivalents (GAEs), respectively, in accordance with previously reported methodologies [11]. Details of the procedures are provided in the supplementary file.

2.3. Evaluation of antioxidant activity

The antioxidant properties of the extracts were assessed using multiple assays: the phosphomolybdenum method for total antioxidant capacity [12], the CUPRAC and FRAP methods for reducing power [13,14], DPPH radical scavenging activity [15], $ABTS^{+\cdot}$ radical scavenging activity [16], and ferrous ion chelation capacity [17]. Antioxidant activity was expressed in two forms: IC_{50} values (indicating the sample concentration required for 50% radical scavenging or ferrous ion chelation, or to achieve an absorbance of 0.500 in reducing power and phosphomolybdenum assays) and as milligrams of standard equivalent per gram of extract. Trolox and disodium EDTA served as positive controls. Detailed protocols can be found in the supplementary file.

2.4. Statistical Analysis

To ensure the reliability of the results, all experiments were conducted in triplicate. Data were presented as the mean ± standard deviation (SD). Statistical analyses were performed using one-way ANOVA with Tukey's honestly significant difference post hoc test and Student's *t*-test, applying a significance level of $\alpha = 0.05$ (SPSS v. 22.0).

3. Results and Discussion

3.1. Qualitative chemical compositions of the extracts

The extraction yields, total phenolic contents (TPC), and total flavonoid contents (TFC) of the methanol and water extracts obtained from *A. cotula* are presented in Table 1. The water extract exhibited a significantly higher extraction yield (19.99%) compared to the methanol extract (11.43%). However, the methanol extract demonstrated superior total phenolic content, with 64.33 mg GAEs/g extract, compared to 56.27 mg GAEs/g extract in the water extract ($p < 0.05$). Similarly, the total flavonoid content was markedly higher in the methanol extract (39.22 mg REs/g extract) than in the water extract (27.98 mg REs/g extract) ($p < 0.05$).

Table 1. Extraction yield, total phenolic and flavonoid contents of the methanol and water extracts from *A. cotula*.

Assays	Methanol	Water
Extraction yield (%)	11.43	19.99
Total phenolics (mg GAEs/g extract)	64.33 ± 0.38^a	56.27 ± 0.57^b
Total flavonoids (mg REs/g extract)	39.22 ± 1.69^a	27.98 ± 0.11^b

The mean values followed by the same superscripts (*a* and *b*) within a row do not differ, according to the Student's t-test at 5% significance level. REs and GAEs rutin and gallic acid equivalents

The results indicate that while the water extract achieved a greater extraction yield, it contained lower levels of both phenolic and flavonoid compounds compared to the methanol extract. This suggests that methanol, as an organic solvent, is more effective in extracting phenolic and flavonoid compounds, likely due to its ability to dissolve a broader range of polar and semi-polar phytochemicals. In contrast, water, being a highly polar solvent, might favor the extraction of hydrophilic compounds but may be less efficient for flavonoids and certain phenolics that exhibit limited solubility in water.

The statistical differences observed between the two extracts highlight the influence of solvent type on the phytochemical composition. Methanol's higher efficiency in extracting bioactive compounds is consistent with its widespread use in studies aimed at maximizing the recovery of secondary metabolites, including phenolics and flavonoids. These findings underscore the importance of solvent selection in optimizing the extraction of specific phytochemicals from medicinal plants and suggest that methanol might be more suitable than water for isolating antioxidant-rich extracts from *A. cotula*.

The analysis of the chemical compositions of water and methanol extracts of *A. cotula* obtained via ultrasound-assisted extraction provides valuable insights into the phytochemical profile of this plant. The findings of the present study are consistent with the results reported by Sut et al. [10], wherein ultrasound-assisted extraction was identified as an efficient method for extracting phenolic compounds and flavonoids, with a high correlation to antioxidant activity. However, the methanol extract in the current study exhibited superior total phenolic content (64.33 mg GAE/g extract) compared to the maximum phenolic content reported by Sut et al. [10] (62.92 mg GAE/g extract using accelerated solvent extraction), suggesting potential variability in the extraction efficiency or plant material origin. Similarly, the methanol extract's total flavonoid content (39.22 mg RE/g extract) exceeded that of ethanol extracts reported by Sabik et al. [18] for *A. cotula* (66.84 mg/g flavonoid content), highlighting the significant influence of extraction solvent and method on yield.

In contrast to Lo'ay et al. [19], who identified apigenin and chlorogenic acid as major phenolic constituents in *A. cotula*, this study did not focus on individual compound identification but emphasized total phenolic and flavonoid content. The observed higher extraction yield in water extracts (19.99%) aligns with Lo'ay et al.'s findings that aqueous extractions often yield higher polar compound concentrations, underlining the versatility of ultrasound-assisted extraction for diverse solvent systems.

The novelty of this work lies in the direct comparison of ultrasound-assisted extraction-derived water and methanol extracts and their statistically significant differences in phenolic and flavonoid contents. Unlike prior studies focusing on essential oils or ethanol-based extractions, this study demonstrates the efficiency of ultrasound-assisted extraction in obtaining phenolic-rich extracts using environmentally benign solvents. Furthermore, the explicit quantification of extraction yield and detailed discussion of solvent effects contribute to the broader understanding of extraction methodologies, laying a foundation for optimized extraction protocols for pharmaceutical applications.

3.2. Antioxidant activities of the extracts

The antioxidant activities of the methanol and water extracts of *A. cotula* were assessed using six different assays, and the results are summarized in Tables 2 and 3.

The methanol extract exhibited significantly higher CUPRAC (262.83 TEs/g extract) and FRAP (154.98 mg TEs/g extract) reducing powers compared to the water extract (235.98 mg TEs/g extract and 127.53 mg TEs/g extract, respectively). The IC_{50} values of the methanol extract for CUPRAC and FRAP assays were also lower (0.41 mg/mL and 0.27 mg/mL, respectively) than those of the water extract (0.46 mg/mL and 0.33 mg/mL, respectively), indicating stronger reducing power activity of the methanol extract.

Both extracts demonstrated high total antioxidant capacities as determined by the phosphomolybdenum assay. The methanol extract had a slightly higher activity (546.61 mg TEs/g extract) than the water extract (535.75 mg TEs/g extract), but this difference was not statistically significant ($p > 0.05$). The IC_{50} values for this assay were comparable for both extracts (0.51 mg/mL for methanol and 0.52 mg/mL for water).

The DPPH and ABTS radical scavenging activities of the methanol and water extracts were also similar, with no significant differences observed between the two

extracts. The methanol extract showed DPPH activity of 83.07 mg TEs/g extract and ABTS activity of 129.87 mg TEs/g extract, while the water extract exhibited activities of 79.66 mg TEs/g extract and 128.58 mg TEs/g extract, respectively. The IC_{50} values for these assays confirmed comparable efficacy, with DPPH IC_{50} values of 2.83 mg/mL (methanol) and 2.95 mg/mL (water) and ABTS IC_{50} values of 1.54 mg/mL (methanol) and 1.56 mg/mL (water).

In contrast to the other assays, the water extract demonstrated superior ferrous ion chelating activity, with a significantly higher activity (12.30 mg EDTAEs/g extract) compared to the methanol extract (8.55 mg EDTAEs/g extract). This trend was consistent with the IC_{50} values, where the water extract (1.06 mg/mL) showed stronger chelating activity than the methanol extract (1.53 mg/mL).

The methanol extract consistently outperformed the water extract in assays related to reducing power (CUPRAC and FRAP) and showed slightly higher radical scavenging activity (DPPH and ABTS). These results can be attributed to the higher total phenolic and flavonoid contents in the methanol extract, as phenolic compounds are well-known for their electron-donating properties, which are crucial for reducing power and free radical scavenging activities. On the other hand, the superior ferrous ion chelating ability of the water extract suggests the presence of other hydrophilic compounds, possibly non-phenolic chelators that are more efficiently extracted in water. While phenolics and flavonoids are key contributors to antioxidant activity, the overall antioxidant potential of a plant extract also depends on the presence of diverse bioactive compounds that may act through different mechanisms.

In summary, the methanol extract of *A. cotula* demonstrated a more robust antioxidant profile in most assays due to its richer phenolic and flavonoid content, while the water extract excelled in ferrous ion chelation, indicating complementary antioxidant properties of the two extracts. These findings highlight the influence of solvent type on the antioxidant potential of plant extracts and underscore the importance of a comprehensive evaluation of multiple antioxidant mechanisms.

The antioxidant activities of the methanol and water extracts obtained from *A. cotula* via ultrasound-assisted extraction revealed notable insights when compared to existing literature, particularly the studies by Sut et al. [10] and Lo'ay et al. [19]. In the current study, the methanol extract demonstrated superior reducing power in CUPRAC and FRAP assays compared to the water extract, consistent with Sut et al. [10], where ultrasound-assisted extraction-derived ethanol extracts showed high reducing capacities. Similarly, the current methanol extract's total antioxidant capacity, as assessed by the phosphomolybdenum assay, aligns closely with findings by Lo'ay et al. [19], where alcoholic extracts (butanol and methanol) exhibited higher activity compared to aqueous extracts.

Table 2. Antioxidant activities of the methanol and water extracts from *A. cotula*.

Assays	Methanol	Water
CUPRAC reducing power (mg TEs/ g extract)	262.83 ± 2.99^a	235.98 ± 5.02^b
FRAP reducing power (mg TEs/ g extract)	154.98 ± 1.13^a	127.53 ± 0.19^b
Phosphomolybdenum (mg TEs/ g extract)	546.61 ± 5.76^a	535.75 ± 9.68^a
DPPH radical scavenging (mg TEs/ g extract)	83.07 ± 2.42^a	79.66 ± 0.66^a
ABTS cation radical scavenging (mg TEs/ g extract)	129.87 ± 0.30^a	128.58 ± 0.91^a
Ferrous ion chelating (mg EDTAEs/ g extract)	8.55 ± 0.72^b	12.30 ± 0.03^a

The mean values followed by the same superscripts (*a* and *b*) within a row do not differ, according to the Student's t-test at 5% significance level. TEs and EDTAEs, trolox and ethylenediaminetetraacetic acid (disodium salt) equivalents, respectively.

Table 3. Effective or inhibition concentration (IC_{50} or EC_{50}: mg/mL) of antioxidant activities of the methanol and water extracts from *A. cotula*.

Assays	Methanol	Water	Trolox	EDTA
CUPRAC reducing power	0.41 ± 0.01^b	0.46 ± 0.01^c	0.11 ± 0.003^a	-
FRAP reducing power	0.27 ± 0.01^b	0.33 ± 0.01^c	0.04 ± 0.001^a	-
Phosphomolybdenum	0.51 ± 0.01^b	0.52 ± 0.01^b	0.28 ± 0.01^a	-
DPPH radical scavenging	2.83 ± 0.08^b	2.95 ± 0.02^b	0.23 ± 0.01^a	-
ABTS cation radical scavenging	1.54 ± 0.01^b	1.56 ± 0.01^b	0.21 ± 0.02^a	-
Ferrous ion chelating	1.53 ± 0.13^c	1.06 ± 0.01^b	-	0.013 ± 0.001^a

The mean values followed by the same superscripts (*a*, *b* and *c*) within a row do not differ, according to the Tukey's honestly significant difference post hoc test at 5% significance level. EC_{50} (mg/mL), effective concentration at which the absorbance was 0.5 for reducing power and phosphomolybdenum assays. IC_{50} (mg/mL), inhibition concentration at which 50% of the DPPH and ABTS radicals were scavenged and the ferrous ion-ferrozine complex were inhibited. EDTA, ethylenediaminetetraacetic acid (disodium salt). "-", not determined

Notably, the present study diverges in ferrous ion chelating activity, where the water extract outperformed the methanol extract. This result contrasts with the general trend in the literature, such as Al-Momani et al. [20], where aqueous extracts were less effective in chelation assays. This discrepancy highlights the potential impact of ultrasound-assisted extraction in preserving hydrophilic chelators during extraction. Furthermore, the observed comparable radical scavenging activities (DPPH and ABTS) between extracts support findings by Sabik et al. [18], where water and methanol extracts exhibited similar antioxidant capacities.

This study provides novel contributions to the literature by demonstrating that ultrasound-assisted extraction enhances the selective extraction of compounds contributing to distinct antioxidant mechanisms. The high ferrous chelating activity of the water extract underscores the potential of ultrasound-assisted extraction to optimize extraction of metal-chelating phytochemicals, a relatively underexplored aspect in *A. cotula*. These findings warrant further investigation into the synergistic effects of phenolics and other bioactive compounds specific to UAE-derived extracts

4. Conclusion

This study highlights *A. cotula* as a promising source of bioactive compounds, particularly phenolics and flavonoids, which are key contributors to its antioxidant potential. The methanol extract showed superior reducing power (CUPRAC and FRAP) and comparable radical scavenging (DPPH and ABTS) and total antioxidant capacity, likely due to its higher phenolic and flavonoid contents. In contrast, the water extract exhibited stronger ferrous ion chelating activity, suggesting the presence of hydrophilic chelating agents. While these findings are significant, further studies are needed to identify specific bioactive compounds using advanced techniques like HPLC or LC-MS and to validate antioxidant activities in biological systems. Additionally, exploring synergistic effects between the extracts and optimizing extraction conditions could enhance their efficacy.

In conclusion, this study underscores the importance of solvent selection in extracting bioactive compounds and establishes *A. cotula* as a potential natural antioxidant source for applications in nutraceuticals or functional foods.

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Author's Contributions

Fatma Özlem Kargın Solmaz: Drafted and wrote the manuscript, performed the experiment and result analysis.

Cengiz Sarıkürkcü: Assisted in analytical analysis on the structure, supervised the experiment's progress, result interpretation and helped in manuscript preparation.

Ethics

There are no ethical issues after the publication of this manuscript.

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