

Phytochemical Composition, Antioxidant Potential, and Computational Analysis of *Delphinium peregrinum* L.

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Abstract

Delphinium peregrinum L. has been traditionally used for its antiparasitic, analgesic, sedative, and antiepileptic properties. This study aimed to investigate the total phenolic (TPC) and flavonoid (TFC) contents, phenolic profiles, antioxidant capacity, and extraction efficiency of *D. peregrinum* cultivated in Uşak, Türkiye. Additionally, molecular docking analysis was conducted to explore the interactions of phenolic compounds with biological targets. Plant samples were collected during the flowering period, and methanol and water extracts were prepared. TPC was found to be 81.566 mg GAE/g in methanol and 83.988 mg GAE/g in water extract, while TFC was 27.006 mg QE/g in methanol and 12.130 mg QE/g in water. Antioxidant activity, assessed via the DPPH assay, revealed 80% and 75% scavenging activity for methanol and water extracts, respectively. HPLC analysis identified key phenolic compounds, including quercetin, coumaric acid, vanillic acid, syringic acid, and ferulic acid. Molecular docking studies focused on the Keap1-Nrf2 complex (PDB ID: 6ZEY), a key regulator of oxidative stress. Quercetin exhibited the strongest binding affinity to Keap1 (-9.4 kcal/mol, Ki: 0.13 µM), followed by coumaric acid (-6.5 kcal/mol, Ki: 17.08 µM). Quercetin also demonstrated a high fit quality score (0.890) and formed a strong hydrogen bonding network with key amino acid residues, suggesting its potential role in modulating oxidative stress pathways. These findings highlight the antioxidant potential of *D. peregrinum*, attributed to its high phenolic and flavonoid content. The strong interaction of quercetin with oxidative stress-related targets further supports its potential in antioxidant defense mechanisms. This study underscores the importance of further pharmacological and nutraceutical research to evaluate the therapeutic potential of *D. peregrinum* and its bioactive constituents.

Introduction

Delphinium peregrinum L. (family Ranunculaceae), commonly known as "Tel Hazeran" is an common species distributed across Türkiye, Southeastern Europe, the Eastern Mediterranean, and the Western Irano-Turanian region. The Ranunculaceae family comprises 43 genera and 2,346 species worldwide, with the genus *Delphinium* represented by approximately 385 species. In Türkiye, this genus includes 31 species, 19 of which are endemic (Çeçen 2021; Cömert et al 2023; *Delphinium Peregrinum* L 2025; Güner et al 2012). *D. Peregrinum* is generally characterized by purple-blue flowers (Fig. 1), although yellowish-brown flowers are rarely observed (Meriçli et al 2009). *D. Peregrinum* have been used in traditional Turkish medicine for their antiparasitic, anthelmintic, analgesic, antirheumatic, sedative, and antiepileptic properties (Baytop 1984; Kolar et al 2014; Ulubelen et al 1998).

Delphinium species contain a wide variety of secondary metabolites, including diterpenoid alkaloids, terpenes, phenolic acids, flavonoids, and essential oils. Particularly rich in diterpenoid alkaloids, these species have recently become a focal point of pharmacological research. Studies have revealed that *Delphinium* species compounds exhibit diverse biological effects, such as anti-inflammatory, analgesic, anticancer, antifungal, cardioprotective, and antiarrhythmic activities. Notably, the antiproliferative activity of natural diterpenoid alkaloids against various human cancer cell lines holds promise for the development of innovative therapeutic strategies in cancer treatment (Alhilal et al 2021; Shakeri et al 2024; X. Wang et al 2024; Yin et al 2020). However, despite these beneficial biological effects of *D. Peregrinum*, diterpenoid alkaloids have been reported to exhibit neurotoxic properties, leading to severe side effects such as motor and sensory loss, paralysis, bradycardia, hypotension, collapse, and even respiratory failure by exerting curare-like effects on both striated and smooth muscles (Adamski et al 2020; Jaoudi et al 2011; Ulubelen et al 1998). This toxicity underscores the need to investigate alternative bioactive components, such as phenolic compounds and flavonoids, in *D. peregrinum*.

Phenolic compounds and flavonoids serve as promising alternatives for bioactive substances in the pharmaceutical and medical fields to enhance human health and to prevent and treat various illnesses through anti-inflammatory properties, antibacterial effects, anticancer properties, and immune system enhancement (Sun and Shahrajabian, 2023). Phenolic compounds are also appreciated for industry in food preservation, cosmetics, packaging, and textiles by their antioxidant, antimicrobial, and coloring abilities. Their natural attributes provide encouraging substitutes for artificial additives, prolonging food longevity and improving product safety. Numerous phenolic substances, such as quercetin, offer UV protection (SPF 7–30). Moreover, their use in natural dye compositions promotes environmentally sustainable practices in the textile sector, minimizing both chemical pollution and allergic responses. In general, the adaptable characteristics of phenolic compounds are leading to their growing use in various industrial sectors (Albuquerque et al 2021). Despite this potential, the phenolic profile and total antioxidant capacity of *D. peregrinum* remain poorly characterized, highlighting a critical gap in the literature.

This study aims to address this gap by conducting a comprehensive evaluation of *D. peregrinum* samples collected from the Uşak region. The evaluation includes quantitative analysis of total phenolic and flavonoid content, HPLC-based identification of phenolic compounds, comparison of extraction efficiencies between methanol and water extracts, and assessment of antioxidant capacity using the DPPH method. By elucidating the phytochemical potential of this species, the study aims to provide valuable data for both pharmacological and industrial applications. Furthermore, examining the effect of different solvents on extraction efficiency offers a methodological perspective that may enhance the development processes of herbal products.

Materials and Methods

Materials

In this study, *Delphinium peregrinum* L., which has purple-blue flowers, was used as the plant material. Plant samples were collected in August 2023 from uncultivated fields in the Ovademirler region of Uşak Province and identified by Dr. Ahmet Kahraman (Uşak University, Faculty of Engineering and Natural Sciences, Department of Molecular Biology and Genetics). The collected specimens are preserved in the Uşak University Plant Systematics and Phylogenetics Laboratory (Herbarium no: B. Özcan and A. Kahraman 2604). The aerial parts of the plant were dried in the shade at room temperature, and then the stems and flowers were ground into powder for analysis.

Chemicals

The study utilized quercetin (QE), gallic acid (GA), sodium acetate trihydrate, aluminum chloride (Sigma-Aldrich Chemie GmbH-Germany), and methanol (Merck-Germany).

Solutions Used for Total Phenolic Content Determination: Sodium carbonate (Na_2CO_3) solution (20%): 20 g of Na_2CO_3 was dissolved in a 100 mL volumetric flask with ultrapure water and stirred until completely dissolved, then diluted to volume to the line of the volumetric flask. Folin-Ciocalteu reagent: A commercially available stock solution was used without dilution.

Solutions Used for Total Flavonoid Content Determination: Aluminum chloride (AlCl_3) solution (10%): 10 g of anhydrous aluminum chloride was dissolved in a 100 mL volumetric flask with ultrapure water and diluted to volume to the line of the volumetric flask. Sodium Acetate (CH_3COONa) solution (1M): 16.5 g of sodium acetate trihydrate was dissolved in a 100 mL volumetric flask with ultrapure water and diluted to volume.

Extraction of Plant Material

The aerial and floral parts of *Delphinium* L. were dried, ground, and homogenized, yielding 50 g of powdered material. A 3 g sample of the powdered mixture was placed in a cellulose extraction cartridge and subjected to Soxhlet extraction using two different solvents: ultrapure water and methanol. The extraction process was carried out for 5 hours to ensure continuous solvent percolation over the sample, which enhances efficiency compared to direct extraction methods involving heating. After extraction, the solvent was evaporated using a rotary evaporator (IKA RV 10), and the obtained extracts were dried in an oven (WiseVen WON105) at 45°C. The final dry extract weights were recorded as 0.948 g for the water extract and 0.911 g for the methanol extract.

Determination of Total Phenolic Content

The total phenolic content (TPC) of the extracts was determined using the Folin-Ciocalteu method with slight modifications. (Gamez-Meza et al 1999). Extract solutions were prepared at a concentration of 500 ppm in methanol. Gallic acid was used as the standard for the calibration curve, with standard solutions prepared at various concentrations (1000, 500, 250, 125, 62.5, 31.25, 15.625, 7.8125 ppm). The absorbance values at 765 nm were plotted against concentration to generate a standard curve, which showed an R^2 value of 0.9999, indicating high precision. For sample analysis, 0.1 mL of extract solution (500 mg /L) was mixed with 7.9 mL of ultrapure water, 0.5 mL of Folin-Ciocalteu reagent, and 1.5 mL of 20% sodium carbonate solution. The mixture was incubated at 40°C for 30 minutes, and absorbance was measured at 765 nm using a UV-Vis spectrophotometer. A blank sample containing only methanol was used as a reference .

Determination of Total Flavonoid Content

Total flavonoid content (TFC) was measured using the aluminum chloride colorimetric method developed by Woisky and Salatino (Woisky and Salatino 1998). Extract solutions were prepared at a concentration of 500 ppm in methanol. Quercetin was used as the standard for the calibration curve, with standard solutions prepared at concentrations of 600, 400, 200, 100, 50, and 25 ppm. The absorbance values at 415 nm were plotted against concentration to generate a standard curve, which showed an R^2 value of 0.9997, confirming the precision of the method. For sample analysis, 0.5 mL of extract solution (500 mg/L) was mixed with 1.5 mL of methanol, 0.1 mL of 10% AlCl_3 solution, and 0.1 mL of 1M sodium acetate solution. The mixture was incubated at room temperature for 30 minutes, and absorbance was measured at 415 nm using a UV-Vis spectrophotometer. A blank sample containing only methanol was used as a reference.

Antioksidan aktivite (DPPH)

The antioxidant activity of the extracts was evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl) assay with modifications based on Thaipong et al. (Thaipong et al 2006). A stock DPPH solution was prepared by dissolving 24 mg of DPPH in methanol and adjusting the final volume to 100 mL. Working solutions were prepared by diluting 20 mL of the stock solution with 90 mL of methanol to achieve an absorbance of 1.1 ± 0.02 at 515 nm. For analysis, 300 μL of plant extract was mixed with 5.7 mL of DPPH working solution and incubated in the dark for 1 hour. Absorbance was measured at 515 nm using a UV-Vis spectrophotometer. Antioxidant activity was calculated using the formula:

$$\% \text{ Antioxidant Activity} = (A_0 - A_1) / A_0 \times 100$$

Where A_0 is the absorbance of the control solution (without extract), and A_1 is the absorbance of the sample. The standard antioxidant (ascorbic acid, 500 ppm) exhibited 98.55% activity, and extract results were compared accordingly. For the plant extract dose study, all parameters were kept constant and tested with five different doses in the plant extract dose range (100 μL -500 μL). The most suitable dose was determined as 300 μL plant extract dose.

HPLC Analysis of Phenolic Compounds

Phenolic compounds were analyzed using an Agilent 1260 HPLC system with an ACE-C18 column (4.6 mm $\times$ 150 mm, 5 μm). The mobile phase consisted of A (0.1% acetic acid in ultrapure water) and B (acetonitrile), with a flow rate of 1.0 mL min^{-1} . The gradient conditions of the mobile phase in HPLC analysis are given in Table 1. The injection volume was set at 10 μL , and the column temperature was maintained at 25°C. Specific wavelengths were selected for the detected phenolic compounds: syringic acid, protocatechuic acid, and gallic acid at 280 nm; vanillic acid at 225 nm; coumaric acid at 305 nm; caffeic acid and chlorogenic acid at 330 nm (Wen et al 2005). Calibration parameters of the analyzed polyphenolic compounds are given in Table 2.

Table 1
HPLC gradient condition of mobile phase

Time (min)	Percentage of solvent	
	A (%)	B (%)
0	92	8
3.25	90	10
8	88	12
15	75	25
15.8	70	30
25	10	90
25.4	0	100
30	0	100

Table 2
Parameters of the calibration of polyphenolic compound

No	Compound	Retention time min.	Equation	Linear range (µg/mL)	R ²	LOD (µg/mL)	LOQ (µg/mL)
1	Gallic acid	2,676 ± 0,010	y = 51,921x + 50,226	5–30	0.9999	1.30	3.90
2	Protocatechic acid	4,328 ± 0,007	y = 36,149x + 56,761	5–30	0.9997	0.80	2.60
3	Chlorogenic acid	6,920 ± 0,005	y = 27,86x + 26,982	5–30	0.9996	1.00	2.90
4	Vanilic acid	7,291 ± 0,004	y = 31,153x + 74,003	5–30	0.9999	0.80	2.40
5	Caffeic acid	7,988 ± 0,004	y = 42,348x + 42,089	5–30	0.9998	1.10	3.30
6	Syringic acid	8,947 ± 0,004	y = 121,46x + 190,72	5–30	0.9996	0.80	2.40
7	Sinapinic acid	12,852 ± 0,003	y = 50,658x + 120,19	5–30	0.9995	0.80	2.40
8	Coumaric acid	14,347 ± 0,003	y = 216,2x + 209,14	5–30	0.9996	0.90	2.90
9	Ferrulic acid	14,620 ± 0,003	y = 104,94x + 164,78	5–30	0.9998	0.80	2.40
10	Quercetin	19,706 ± 0,002	y = 10,505x + 16,498	5–30	0.9997	0.80	2.40

Medicinal Chemistry and ADMET Analysis Method

The pharmacokinetic and medicinal chemistry properties of Quercetin and Coumaric acid were analyzed using ADMETlab 3.0 (<https://admetlab3.scbdd.com/>). This platform provides a comprehensive assessment of drug-likeness, bioavailability, and toxicity-related parameters. The SMILES representations of the compounds were retrieved from the PubChem database and uploaded to the system for computational analysis. Various medicinal chemistry descriptors were evaluated, including quantitative estimate of drug-likeness (QED), synthetic accessibility scores (SAscore, GASA), fraction of sp³-hybridized carbons (Fsp³), molecular complexity (MCE-18), natural product-likeness (NPscore), compliance with Lipinski and GSK rules, the Golden Triangle rule, colloidal aggregation risk, luciferase inhibition (FLuc), fluorescence properties (blue and green fluorescence), reactivity potential, promiscuity assessment, PAINS (Pan-Assay Interference Compounds) filter, and the Chelating Rule for metal complexation propensity. The PAINS filter was applied to identify compounds prone to assay interference, while the Chelating Rule assessed their potential for metal ion chelation. These analyses provided insights into the drug-likeness, bioavailability potential, and stability of the compounds in biological systems.

Computational details

Ligand Preparation

The major phytochemicals derived from plant extracts were obtained from the PubChem database. In this study, molecular structures in "sdf" format were converted to "pdb" format using Discovery Studio Visualizer software. To assess the conformational flexibility of the ligands, torsional adjustments were applied. The PyRx software, specifically the AutoDock Vina toolset, was utilized to generate "pdbqt" files required for molecular docking simulations.

Receptor Preparation

The crystal structure of 6ZEY, representing the Keap1 Kelch domain in complex with a small-molecule inhibitor targeting the Keap1-Nrf2 protein-protein interaction, was retrieved from the RCSB Protein Data Bank (<https://www.rcsb.org/>). To prepare the receptor for docking studies, structural modifications

were performed, including the removal of water molecules, atom replacements, and charge assignments. The final pdbqt file required for molecular docking was generated using the AutoDock 4.2 software package.

Molecular Docking and Binding Energy Analysis

In this study, protein and ligand preparation was conducted using AutoDock tools, employing specialized modules and algorithms to ensure precision and reliability. The docking simulations were performed to identify the most stable binding conformation. To determine the optimal ligand-receptor interaction, docking poses were evaluated, and the complex with the lowest binding energy was selected for further analysis. Visualization and post-docking refinement were carried out using Discovery Studio Visualizer to validate the structural interactions and confirm stability (Trott and Olson 2010)

Statistical Analysis

All experiments were conducted in triplicate, and data were presented as mean ± standard error. Differences between methanol and water extracts were assessed using an independent t-test, with statistical significance set at p < 0.05.

Results and Discussion

Plants exhibit their pharmacological effects through various phytochemical compounds such as polyphenols, flavonoids, phenolic acids, fatty acids, and alkaloids. Among these compounds, polyphenols (flavonoids, phenols, and phenolic acids) constitute the largest and biologically significant group of phytochemicals synthesized in plants (Zagoskina et al., 2023). There is no study in the literature regarding the total phenolic or flavonoid compound content of *D. peregrinum*, and existing studies on this species have focused solely on alkaloid analysis. These studies have identified alkaloids such as peregrine, 14-acetylperegrine, 10-hydroxyperegrine, delphiperegrine, 14-O-benzoylperegrine, 14-O-methylperegrine, and α-atizine in *D. peregrinum* (Soydan and Meriçli 2009).

Extraction Yield

In the analyses, 3 g of powdered sample was used for each extraction. The extraction process using pure water yielded 0.948 g of dry extract with an efficiency of 30.93%, while the extraction using methanol yielded 0.911 g of dry extract with an efficiency of 29.53% (Table 4).

Table 4 The profile of phenolic asits <i>D. peregrinum</i> in metanol and water extract (mg/g dry extract).												
	Quercetin	Cumaric acid	Ferrulic acid	Vanilic acid	Siringic acid	Gallic acid	Protocatechic acid	Gentisic acid	Chlorogenic acid	Catechic acid	Cafeic acid	Sinapinic acid
Methanol extract	2,21	0,112	0,071	0,098	0,077	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	±	±	±	±	± 0,001							
	0,23	0,002	0,001	0,002								
Water extract	0,68	0,031	0,043	0,084	0,064	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	± 0,15	±	±	±	± 0,001							
		0,001	0,001	0,001								
N.D.: Nondefined												

Total Phenolic Content (TPC)

The TPC was determined to be 81.57 ± 0.16 mg GAE/g dry extract for the methanol extraction and 83.99 ± 0.17 mg GAE/g dry extract for the pure water extraction. The TPC was found to be higher in the sample extracted with pure water (Table 3). The difference between the two was statistically significant (p < 0.001). Studies conducted on different species of the *Delphinium* genus reveal that these species have significant potential in terms of phenolic content, and extraction methods have a notable impact on this content. For instance, analyses conducted on *Delphinium malabaricum* (Huth) Munz determined that water extraction yielded a total phenolic content of 13.4 ± 0.72 mg GAE/g in roots and 8.08 ± 0.22 mg GAE/g in leaves. In methanol extraction, these values were measured as 9.48 ± 0.21 mg GAE/g in roots and 3.38 ± 0.43 mg GAE/g in leaves (Kolar et al 2014). Similarly, a study on the flowers of *Delphinium grandiflorum* L. reported a total phenolic content of 13.38 mg GAE/g in ethanol extract and 13.37 mg GAE/g in water extract (Dahyun et al 2023). Another significant finding was reported in *Delphinium denudatum* Wall., where methanol extract of leaves contained 80.52 mg GAE/g of total phenolic content, the highest value recorded among seven differe nt solvents (Kumari et al 2024). In another study on the same species, methanol extract contained 90.43 ± 0.07 mg GAE /g, while the water extract contained 67.54 ± 0.53 mg GAE/g (Siddique 2025). The total phenolic content in ethanol extract from the aerial parts of *Delphinium elbursense* Rech.f. was reported as 52.24 ± 1.7 mg GAE/g (Ebrahimzadeh et al 2010). Notably, in *Delphinium uncinatum* Wall., methanol extraction resulted in a remarkably high phenolic content of 298.2 ± 11.9 mg GAE/g, indicating the species’ richness in phenolic compounds (Rehman et al 2023). Similarly, *D. peregrinum* analysis yielded 83.99 ± 0.17 mg GAE/g in water extraction and 81.57 ± 0.16 mg GAE/g in methanol extraction. The findings indicate that both methanol and water extracts exhibit a significantly high phenolic content. Although the phenolic content in water extract is slightly higher than in methanol extract, the values are quite close to each other, suggesting that the plant is rich in water-soluble components. These findings collectively demonstrate that species of the *Delphinium* genus are a rich source of phenolic compounds and that extraction methods have a significant influence on phenolic content..

Table 3
Total phenolic, total flavonoid content and extract yield of *D. peregrinum*

<i>D. peregrinum</i>	Solvent	Extraction Yield (%)	Total Phenolic Substance Amount (mg GAE/ g dry extract)	Total Flavonoid Substance Amount (mg QE /g dry extract)	DPPH % Inhibisyon
	Methanol	29,53	81.57 ± 0,16	27.01 ± 0,04	80
	Water	30,93	83.99 ± 0,17	12.13 ± 0,02	75

Total Flavonoid Content (TFC)

The TFC was determined to be 27.01 ± 0.04 mg QE/g dry extract for the methanol extraction and 12.13 ± 0.02 mg QE/g dry extract for the pure water extraction. The TFC was found to be higher in the sample extracted with methanol (Table 3). The difference between the two was statistically significant ($p < 0.001$). When examining studies on the total flavonoid content of *Delphinium* species, considerable variations were observed depending on different species and extraction methods. In *D. malabaricum*, water extract analysis revealed flavonoid content of 7.88 ± 0.08 mg QE/g in leaves and 6.08 ± 0.70 mg QE/g in roots, whereas methanol extract contained 7.05 ± 0.36 mg QE/g in leaves and 1.19 ± 0.23 mg QE/g in roots (Kolar et al 2014). A study on *D. denudatum* reported 38 mg QE/g in methanol extract and 57.53 mg QE/g in acetone extract (Kumari et al., 2024). Another study on the same species detected flavonoid contents of 5.72 ± 0.37 mg QE/g in methanol extract and 4.98 ± 0.27 mg QE/g in water extract (Kumari et al 2024). Aynı türle ilgili başka bir çalışmada ise metanol ekstresinde 5.72 ± 0.37 mg QE/g ve su ekstresinde 4.98 ± 0.27 mg QE/g flavonoid içeriği tespit edilmiştir (Siddique 2025). In *D. elbursense*, the flavonoid content in ethanol extract was reported as 17.26 ± 0.6 mg QE/g (Ebrahimzadeh et al 2010). Meanwhile, *D. uncinatum*, known for its high phenolic content, exhibited a remarkably high total flavonoid content of 71 ± 5.6 mg QE/g (Rehman et al 2023).

In *D. peregrinum*, total flavonoid content was determined as 27.01 ± 0.04 mg QE/g in methanol extract and 12.13 ± 0.02 mg QE/g in water extract, indicating that methanol extraction is more efficient for flavonoid yield. The higher flavonoid concentration in *D. malabaricum*'s water extract suggests that this species contains a high proportion of water-soluble flavonoid components. In contrast, the higher concentration of methanol-soluble flavonoid compounds in *D. peregrinum* suggests a species-specific affinity for methanol-soluble flavonoid compounds. Additionally, the total flavonoid content was found to be lower than the total phenolic content, likely due to variations influenced by species type, developmental stage, and environmental conditions.

Antioxidant Activity (DPPH)

The DPPH free radical scavenging activity was 80% for the methanol extract and 75% for the water extract. The DPPH activity of the methanol extract was higher than that of the water extract (Table 3). The difference between the two was statistically significant ($p < 0.001$). In the phenolic compound analysis of *D. peregrinum*, the most abundant flavonoid detected was quercetin. It was found at a concentration of 2.21 ± 0.23 mg/g in the methanol extract, whereas in the water extract it was significantly lower at 0.68 ± 0.15 mg/g. Studies have demonstrated that both the amount of quercetin and its antioxidant capacity vary considerably depending on the solvent used. In particular, polar solvents such as water, methanol, and ethanol can dissolve quercetin more effectively by forming hydrogen bonds, while its solubility is limited in pure water. This limitation results in a decrease in both the quercetin content and the antioxidant capacity, highlighting the importance of optimizing the solvent system. In this regard, mixed solvent systems, such as water-ethanol or water-methanol, have been suggested as more effective alternatives (Pinelo et al 2004). The difference in quercetin content observed in this study is considered to be attributable to the difference in solvents.

Quercetin, which possesses a wide range of biological activities, exhibits strong antioxidant properties along with anti-inflammatory, anti-aging, anticancer, anti-obesity, antiviral, antibacterial, antiallergic, and antiatherosclerotic effects (G. Wang et al 2022). This flavonoid, derived from natural sources, is present in high amounts in many plants, including capers, red onions, cabbage, blueberries, watercress, grapes, apples, tomatoes, tea, St. John's wort, and gotu kola (El-Saber Batiha et al 2020). Therefore, the quercetin content in *D. peregrinum* reflects the plant's potential pharmacological and therapeutic value. Other phenolic acids identified in *D. peregrinum* include coumaric acid, ferulic acid, vanillic acid, and syringic acid. Several studies have shown that these phenolic compounds possess multiple activities, such as antioxidant, anti-inflammatory, and anticancer effects (Gortzi et al 2024; Kaur et al 2022; Roychoudhury et al 2021; Srinivasulu et al 2018). The presence of these secondary metabolites suggests that *D. peregrinum* could serve as a valuable resource in these areas, although further studies are needed.

HPLC Analysis Results for Phenolic Compounds

HPLC analysis for the identification of phenolic acid compounds revealed the following: In the methanol extract: quercetin (2.21 ± 0.23 mg/g), coumaric acid (0.112 ± 0.002 mg /g), ferulic acid (0.071 ± 0.001 mg/g), vanillic acid (0.098 ± 0.002 mg/g), and syringic acid (0.077 ± 0.001 mg/g). In the water extract: quercetin (0.68 ± 0.15 mg/g), coumaric acid (0.031 ± 0.001 mg/g), ferulic acid (0.043 ± 0.001 mg/g), vanillic acid (0.084 ± 0.001 mg/g), and syringic acid (0.064 ± 0.001 mg/g). Gallic acid, protocatechuic acid, gentisic acid, chlorogenic acid, catechin, caffeic acid, sinapic acid, ellagic acid, succinic acid, carboxylic acid, and galacturonic acid were not detected in either extract. According to the results, quercetin was found in the highest amount (2.21 ± 0.23 mg/g) in the methanol extract, and the levels of all analyzed compounds were higher in the methanol extract compared to the water extract (Table 4). According to the antioxidant activity results evaluated using the DPPH method, *D. peregrinum* exhibited high antioxidant activity, with inhibition rates of 80% in the methanol extract and 75% in the water extract. Similarly, in a study conducted on *D. denudatum* using the FRAP method, the antioxidant capacity of the methanol extract (94.38 ± 0.56 mgA/g) was reported to be higher than that of the water extract (71.38 ± 0.78 mgA/g) (Kumari et al 2024). In contrast, for *D. malabaricum*, the inhibition rates in the roots and leaves were determined as 76.03% and 55.10% in the water extract, and 73.97% and 33.12% in the methanol extract, respectively (Kolar et al 2014). In *D. peregrinum*, the DPPH radical scavenging activity was found to be higher in the methanol extract compared to the water extract. The stronger antioxidant effect of the methanol extract is attributed to its higher total phenolic and flavonoid contents.

Moreover, the greater amount of quercetin, a compound known for its high antioxidant activity, in the methanol extract is expected to contribute significantly to this enhanced effect. These results indicate that different solvents have a considerable impact on the antioxidant capacity of plant extracts.

Polyphenols have been shown to act as antioxidants by enhancing the activity of antioxidant vitamins and enzymes in combating oxidative stress induced by reactive oxygen species (ROS). Furthermore, the biological effects and health benefits of polyphenols have been widely studied, with evidence suggesting their therapeutic potential in treating various diseases, particularly cancer, cardiovascular diseases, and neurodegenerative disorders. It has also been reported that the antioxidant properties of phenolic compounds help prevent apoptosis triggered by oxidative stress (Lang et al 2024; Rudrapal et al 2022; Şen et al 2010). Several studies have identified a positive correlation between the total phenolic content (TPC) in plants and their measured antioxidant capacity (Mustafa et al 2010). For instance, a study of extracts from 133 Indian medicinal plants reported a high correlation ($R = 0.9378$) between TPC and antioxidant activity measured using the DPPH method (Surveswaran et al 2007). These correlations underscore the usefulness of total phenolic content as an indicator of the overall reducing capacity and antioxidant potential in plants and foodstuffs. In other words, the phenolic content obtained from a plant also reflects its antioxidant capacity (Büyüktüncel 2014). In summary, the high levels of phenolic and flavonoid compounds obtained from *D. Peregrinum*, particularly the substantial presence of quercetin with its potent antioxidant properties, indicate the plant's considerable potential antioxidant capacity.

ADMETlab 3.0 and Molecular Docking

The medicinal chemistry and drug-likeness properties of Quercetin and Coumaric acid were analyzed using ADMETlab 3.0. The QED (Quantitative Estimate of Drug-likeness) values indicate that Coumaric acid (0.651) has a higher drug-likeness potential compared to Quercetin (0.434) (Table 5). Both compounds were classified as easily synthesizable based on SAScore and GASA evaluations. The Fsp³ value for both molecules was determined as 0.0, indicating a predominantly planar structure with a high degree of aromaticity. Molecular complexity (MCE-18) was found to be higher for Quercetin (19.0) compared to Coumaric acid (6.0), suggesting a structurally more intricate framework. Additionally, the Natural Product Score (NPscore) was higher for Quercetin (1.701) than Coumaric acid (0.841), reflecting Quercetin's closer resemblance to naturally occurring compounds.

Table 5
Medicinal Chemistry and Drug-Likeness Properties of Quercetin and Coumaric Acid

ADMETlab 3.0(Medicinal Chemistry)	Quercetin	Cumaric acid
QED	0.434	0.651
SAscore	Easy	Easy
GASA	Easy	Easy
Fsp ³	0.0	0.0
MCE-18	19.0	6.0
NPscore	1.701	0.841
Lipinski Rule	Accepted	Accepted
GSK Rule	Accepted	Accepted
GoldenTriangle	Accepted	Accepted
Colloidal aggregators	0.891	0.287
FLuc inhibitors	0.542	0.999
Blue fluorescence	0.931	0.023
Green fluorescence	0.217	0.158
Reactive compounds	0.698	0.999
Promiscuous compounds	0.921	0.881

Both compounds complied with the Lipinski and GSK rules, indicating favorable pharmacokinetic properties. The Golden Triangle criterion confirmed their balanced physicochemical attributes for drug development. The colloidal aggregation risk was lower for Coumaric acid (0.287) compared to Quercetin (0.891), suggesting that Coumaric acid may yield more reliable results in biological assays. FLuc inhibition was notably high for Coumaric acid (0.999), raising concerns about potential assay interference.

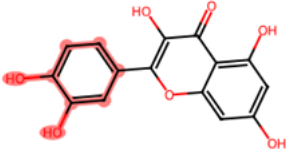
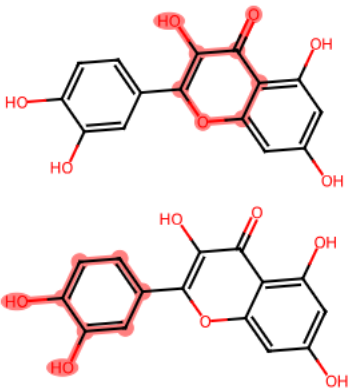
In terms of fluorescence properties, Quercetin exhibited higher blue (0.931) and green fluorescence (0.217) than Coumaric acid (0.023 and 0.158, respectively), indicating a greater potential for optical signal interference in fluorescence-based assays. Reactivity analysis revealed that Coumaric acid (0.999) has a significantly higher reactivity score than Quercetin (0.698), implying a greater likelihood of undergoing chemical transformations and side reactions in biological environments. The promiscuity score, which indicates the potential for interaction with multiple biological targets, was found to be high for both compounds (Quercetin: 0.921, Coumaric acid: 0.881), suggesting broad target engagement.

Overall, Coumaric acid exhibits more favorable drug-likeness properties, yet its high reactivity and FLuc inhibition potential necessitate careful consideration in biological assays. Conversely, Quercetin demonstrates greater molecular complexity and natural product resemblance but is associated with higher

aggregation and optical interference risks. These findings underscore the need for comprehensive pharmacokinetic and pharmacodynamic evaluations before considering these compounds for further drug development studies.

The assessment of PAINS (Pan-Assay Interference Compounds) filter and chelation potential (Chelating Rule) for Quercetin and Coumaric acid was conducted to determine their reliability in biological assays and their tendency to interact with metal ions (Table 6). The PAINS filter is a crucial parameter for identifying structural motifs that may lead to false-positive results in biological experiments. The results indicate that Quercetin received one PAINS alert, whereas Coumaric acid did not trigger any PAINS warnings. This suggests that Coumaric acid may yield more reliable results in biological assays, while Quercetin might contain reactive groups that could interfere with experimental outcomes.

Table 6 PAINS and Chelation Potential of Quercetin and Coumaric Acid

	PAINS	Chelating Rule
Quercetin	1	2
		
Coumaric acid	0	0

The Chelating Rule was applied to assess the ability of these compounds to form complexes with metal ions, which is essential for understanding their interactions with metal-dependent enzymes and biological pathways. The results show that Quercetin has a chelation score of 2, indicating a strong potential for metal ion binding, which could influence enzymatic functions or biochemical processes. In contrast, Coumaric acid scored 0, suggesting a negligible tendency for chelation and a more stable profile in metal-rich biological environments.

Overall, these findings suggest that Quercetin exhibits a significant capacity for metal ion binding, which could be beneficial for certain therapeutic applications but may also introduce potential side effects in biological systems. On the other hand, Coumaric acid, with its lack of PAINS alerts and negligible chelating ability, appears to have a more reliable pharmacokinetic profile.

The binding interactions of Quercetin and Coumaric acid with the target protein were evaluated using molecular docking analysis (Table 7). Binding energy (kcal/mol) is a crucial parameter that determines the stability of ligand-protein interactions. The results indicate that Quercetin exhibits a binding energy of -9.4 kcal/mol, whereas Coumaric acid shows a binding energy of -6.5 kcal/mol, suggesting that Quercetin has a stronger binding affinity toward the target protein.

Table 7
Results of binding interactions of the compounds with target 6ZEY

	Binding Energy (kcal/mol)	Ligand efficiency	Fit quality (FQ)	Estimated Inhibition constant {(Ki) (μM)}	pIC ₅₀
Quercetin	-9.4	0.427	0.890	0.13	6.710
Coumaric acid	-6.5	0.542	0.500	17.08	4.650

Ligand efficiency (LE) was also assessed, revealing that Coumaric acid (0.542) has a higher efficiency than Quercetin (0.427). However, when examining the Fit Quality (FQ) values, Quercetin (0.890) outperforms Coumaric acid (0.500), indicating that despite its lower ligand efficiency, Quercetin demonstrates a better overall binding fit to the target protein.

The estimated inhibition constant (Ki), which reflects the binding strength of the compounds, was calculated as 0.13 μM for Quercetin and 17.08 μM for Coumaric acid. Since lower Ki values indicate stronger inhibitory potential, Quercetin is predicted to be a more potent inhibitor compared to Coumaric acid.

Furthermore, pIC50 values, which indicate the potential inhibitory activity of the compounds, were found to be 6.710 for Quercetin and 4.650 for Coumaric acid, reinforcing the notion that Quercetin exhibits greater biological activity. Overall, these findings suggest that Quercetin has a stronger binding affinity and inhibitory effect on the target protein, whereas Coumaric acid demonstrates higher ligand efficiency but a lower binding strength.

The molecular interactions between Quercetin and Coumaric acid with the target protein were analyzed using molecular docking studies (Table 8). The interaction types were classified based on hydrogen bonds, carbon-hydrogen bonds, and π -alkyl interactions, which contribute to the overall binding stability. Hydrogen bonding plays a crucial role in stabilizing ligand-protein interactions. For Quercetin, conventional hydrogen bonds were observed with VAL465, VAL512, VAL606, GLY367, and ALA510 residues (Fig. 2A). The DHA (donor-hydrogen-acceptor) angles for these interactions ranged from 146.495° to 174.626°, while the HAY (hydrogen-acceptor-yaw) angles varied between 105.067° and 162.786°, indicating strong hydrogen bond formation with the target protein. Additionally, carbon-hydrogen bond interactions were detected with ARG415 and GLY464 residues, with bond angles ranging from 112.336° to 136.499°, further contributing to ligand stabilization. Furthermore, π -alkyl interactions were observed with ALA366 and ALA556 residues, indicating hydrophobic interactions that may enhance ligand binding affinity. For Coumaric acid, conventional hydrogen bonds were observed with GLY509 and VAL465 residues, with DHA angles ranging from 114.521° to 171.718° and HAY angles between 102.468° and 123.511° (Fig. 2B). Additionally, a π -donor hydrogen bond was formed with VAL465, suggesting a different binding mechanism compared to Quercetin. Moreover, π -alkyl interactions were detected with ALA366 and VAL465 residues, indicating potential hydrophobic interactions. Overall, Quercetin demonstrated a higher number of hydrogen bonds and carbon-hydrogen interactions, with a broader angular distribution, indicating a more stable binding interaction with the target protein. In contrast, Coumaric acid exhibited fewer hydrogen bonds but compensated with π -alkyl and π -donor hydrogen interactions, which may contribute to its binding stability in specific regions of the protein. These findings suggest that while both compounds have the potential to interact with the target protein, Quercetin forms stronger and more stable interactions due to its extensive hydrogen bonding network.

Components	Interaction Pair	Bond Type	Angle DHA (°)	Angle HAY (°)
Quercetin	A:VAL465:HN - :[001:O4	Conventional Hydrogen Bond	153.257	131.358
	A:VAL512:HN - :[001:O4	Conventional Hydrogen Bond	146.495	105.067
	A:VAL606:HN - :[001:O2	Conventional Hydrogen Bond	166.66	116.398
	: [001:H2 - A:GLY367:O	Conventional Hydrogen Bond	168.569	120.788
	: [001:H4 - A:VAL512:O	Conventional Hydrogen Bond	155.815	162.786
	: [001:H5 - A:ALA510:O	Conventional Hydrogen Bond	174.626	151.852
	A:ARG415:HA - :[001:O7	Carbon Hydrogen Bond	112.336	119.31
	A:GLY464:HA1 - :[001:O4	Carbon Hydrogen Bond	136.463	104.079
	A:GLY464:HA1 - :[001:O5	Carbon Hydrogen Bond	136.499	107.737
	: [001 - A:ALA366	Pi-Alkyl	-	-
	: [001 - A:ALA556	Pi-Alkyl	-	-
Cumaric acid	: [001:H1 - A:GLY509:O	Conventional Hydrogen Bond	114.521	102.468
	: [001:H6 - A:VAL465:O	Conventional Hydrogen Bond	171.718	123.511
	A:VAL465:HN - :[001	Pi-Donor Hydrogen Bond	-	-
	: [001 - A:ALA366	Pi-Alkyl	-	-
	: [001 - A:VAL465	Pi-Alkyl	-	-

Conclusion

In this study, the total phenolic and flavonoid contents, phenolic compound profile, and antioxidant capacity of *D. peregrinum* were systematically analyzed using different solvents for the first time. The methanol extract contained 81.566 mg GAE/g total phenolics and 27.006 mgQE/g total flavonoids, while the water extract contained 83.988 mg GAE/g and 12.130 mgQE/g, respectively. The DPPH assay demonstrated 80% antioxidant activity for the methanol extract and 75% for the water extract. HPLC analysis identified key bioactive compounds, including quercetin, coumaric acid, vanillic acid, syringic acid, and ferulic acid, highlighting the plant’s rich phytochemical composition and potential as a natural antioxidant source. Molecular docking studies further confirmed the bioactivity of these phenolic compounds, particularly quercetin and coumaric acid, which exhibited strong binding affinities with the Keap1 protein (PDB ID: 6ZEY). Quercetin demonstrated the highest binding energy (-9.4 kcal/mol, Ki: 0.13 μ M), followed by coumaric acid (-6.5 kcal/mol, Ki: 17.08 μ M), suggesting their potential role in modulating oxidative stress-related pathways. Additionally, ADMET predictions provided insights into their pharmacokinetic properties, indicating favorable drug-likeness scores while highlighting certain absorption and metabolism-related considerations that require further investigation. Despite the promising phytochemical profile of *D. peregrinum*, the toxic properties associated with its diterpenoid alkaloids, particularly their neurotoxic effects, should not be overlooked. Therefore, it is crucial to conduct detailed analyses, isolate active compounds responsible for antioxidant and pharmacological activities, and elucidate their biological effects through experimental studies. The integration of computational approaches, including molecular docking and ADMET predictions, offers valuable preliminary insights into the potential therapeutic applications of *D. peregrinum* and its bioactive constituents, paving the way for further pharmacological evaluations.

Declarations

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Author contributions: Conceptualization: BO, MUY, NS, MRD, IB, ECA and EOS; Methodology: BO, MUY, NS, MRD, IB, ECA and EOS; Formal analysis and investigation: NS, MRD, IB, EOS, ECA; Writing - original draft preparation: BO, NS, MRD, ECA; Writing - review and editing: BO, MUY, EOS, ECA; Resources: BO; Supervision: MUY, EOS. All authors reviewed the manuscript.

Data Availability: No datasets were generated or analysed during the current study.

Ethical Declaration: Not applicable.

Consent for Publication: Not Applicable.

Competing Interests: The authors declare no competing interests.

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Figures



Figure 1

Delphinium peregrinum L. (Tel hazeran) stems and flowers

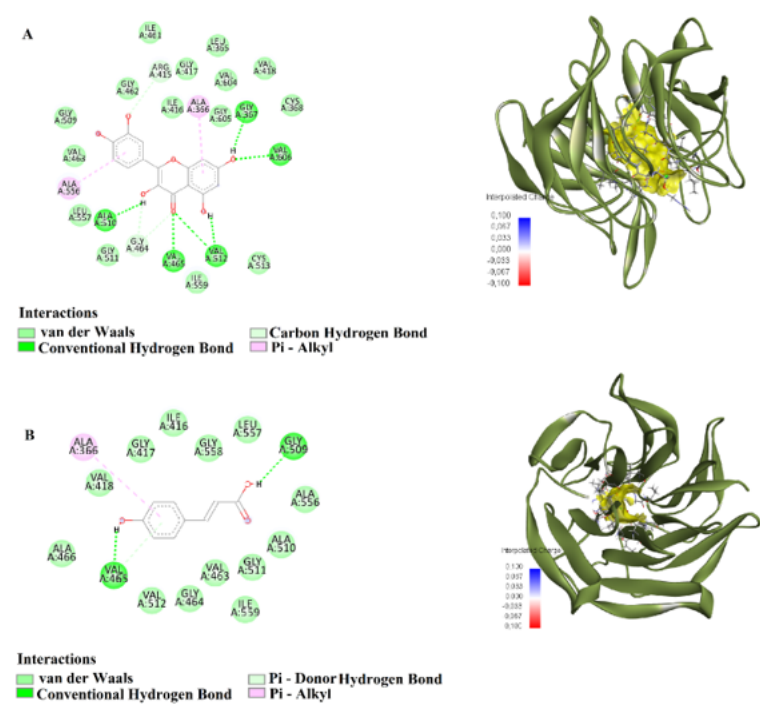


Figure 2

2D and 3D molecular docking interaction analysis of quercetin (A) and coumaric acid (B) with the Keap1 (6ZEY) binding site.