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Phytochemical Characterisation and Antioxidant Potential of *Peganum harmala* L. Seeds: A Natural Source of Bioactive Compounds

Muammer TEPE[1*]

[1] Manisa Celal Bayar University, Akhisar Vocational School, Department of Chemical Processing Technologies, Manisa, Türkiye

**Corresponding author: muammer.tepe@cbu.edu.tr*

Abstract

This study investigated the antioxidant potential and biochemical composition of Peganum harmala (üzerlik) using ethanol (ETOH) and water (AQUA) as extraction solvents. Antioxidant capacity was assessed via ABTS, DPPH, and FRAP assays, alongside total protein quantification and chromatographic analysis of phenolic compounds. The ethanol extract demonstrated markedly higher ABTS (782 µM TE/gDW) and DPPH (150 µM TE/gDW) activities compared to the aqueous extract (160.25 and 60.94 µM TE/gDW, respectively), indicating ethanol's greater efficiency in extracting lipophilic antioxidants. Conversely, FRAP activity was higher in the aqueous extract (684.69 µM TE/gDW) than in ethanol (520.69 µM TE/gDW), suggesting better recovery of hydrophilic antioxidants. Protein content was also higher in ethanol extracts (54.41 µg/gDW) than in aqueous (39.37 µg/gDW). Phenolic profiling revealed that aqueous extracts were richer in 3-hydroxybenzoic, 4-hydroxybenzoic, ferulic, and p-coumaric acids, while ethanol extracts contained gallic and chlorogenic acids absent in aqueous samples. Flavonoids such as hesperidin and hyperoside were detected only in the aqueous extract. Overall, ethanol favored the extraction of proteins, lipophilic antioxidants, and certain phenolic acids, while water was more effective for hydrophilic phenolics and some flavonoids. These findings underscore the solvent-dependent selectivity in bioactive compound recovery from P. harmala, providing a comprehensive insight into its functional potential.

Keywords

Peganum harmala L.,
Antioxidant activity,
Phenolic compounds,
Ethanol and water extraction,
Protein content

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Peganum harmala L. Tohumlarının Fitokimyasal Karakterizasyonu ve Antioksidan Potansiyeli: Biyoaktif Bileşiklerin Doğal Bir Kaynağı

Muammer TEPE[1*]

[1]Manisa Celal Bayar Üniversitesi, Akhisar Meslek Yüksekokulu, Kimya ve Kimyasal İşleme Teknolojileri Bölümü, Manisa, Türkiye

Sorumlu yazar: muammer.tepe@cbu.edu.tr

Özet

Bu çalışmada, Peganum harmala (üzerlik) bitkisinin antioksidan potansiyeli ve biyokimyasal bileşimi, çözücü olarak etanol (ETOH) ve su (AQUA) kullanılarak değerlendirilmiştir. Antioksidan kapasite ABTS, DPPH ve FRAP yöntemleriyle belirlenmiş; toplam protein miktarı ile fenolik bileşik profili kromatografik analizlerle incelenmiştir. Etanol ekstraktı, ABTS (782 µM TE/gKM) ve DPPH (150 µM TE/gKM) aktivitelerinde sulu ekstrakta (160,25 ve 60,94 µM TE/gKM) kıyasla belirgin üstünlük göstermiş, bu da lipofilik antioksidanların ekstraksiyonunda etanolün daha verimli olduğunu ortaya koymuştur. Buna karşın, FRAP aktivitesi sulu ekstrakta (684,69 µM TE/gKM) etanol ekstraktına (520,69 µM TE/gKM) göre daha yüksek bulunmuş ve hidrofilik antioksidanların su ile daha iyi ekstrakte edildiğini göstermiştir. Protein içeriği de etanol ekstraktında (54,41 µg/gKM) sulu ekstrakta (39,37 µg/gKM) göre daha yüksek tespit edilmiştir. Fenolik profil analizinde, sulu ekstraktın 3-hidroksibenzoik, 4-hidroksibenzoik, ferulik ve p-kumarik asit bakımından zengin olduğu; etanol ekstraktında ise sulu örneklerde bulunmayan gallik ve klorojenik asit tespit edilmiştir. Ayrıca, hesperidin ve hiperosid yalnızca sulu ekstrakta belirlenmiştir. Bulgular, P. harmala'da çözücüye bağlı biyoaktif bileşik seçiciliğini ortaya koymakta ve fonksiyonel potansiyeli hakkında kapsamlı bilgi sunmaktadır.

Anahtar kelimeler

Peganum harmala L., Antioksidan aktivite, Fenolik bileşikler, Etanol ve su ekstaksiyonu, Protein içeriği

1. INTRODUCTION

Peganum harmala L. (Syrian Rue) is a perennial herbaceous plant belonging to the Zygophyllaceae family, widely distributed in arid and semi-arid regions across the Middle East, North Africa, and Central Asia [1,2]. This species has been extensively studied due to its remarkable adaptability to harsh environments and its longstanding use in traditional medicine systems. The plant is characterized by its small, fleshy leaves and distinctive white to pale pink flowers, with fruiting bodies producing seeds that are notably rich in bioactive compounds [3,4].

Figure 1. Seasonal changes of P. harmala plant a) Fresh plant b) Dry plant c) Dry seed

The seeds of P. harmala are particularly significant as they contain high concentrations of alkaloids, primarily beta-carbolines such as harmine, harmaline, and harmalol, which are responsible for many of the plant's pharmacological properties [5,6]. These alkaloids have demonstrated diverse biological activities including monoamine oxidase (MAO) inhibition, neuroprotective effects, vasorelaxation, antimicrobial, and antiparasitic actions [7–10]. Beyond alkaloids, P. harmala seeds also possess a complex phytochemical profile comprising phenolic compounds, flavonoids, proteins, and essential oils, which contribute synergistically to their antioxidant and therapeutic potential [11–14].

The phenolic content and antioxidant capacity of P. harmala seeds have been correlated with protective effects against oxidative stress, which is implicated in the pathogenesis of various chronic diseases [15–17]. Furthermore, the protein content in the seeds offers additional nutritional and functional value, potentially enhancing their bioactivity [18]. Despite these insights, comprehensive analyses that integrate the phytochemical characterisation with detailed evaluations of biological activities remain limited.

Therefore, the present study aims to investigate the biochemical composition of Peganum harmala seeds, focusing on alkaloid, phenolic, and protein contents, alongside assessing their antioxidant capacity and related pharmacological effects. This approach seeks to elucidate the underlying mechanisms that support the traditional uses of P. harmala and to evaluate its potential as a source of natural therapeutic agents.

2. MATERIAL and METHODS

2.1. Extraction Methods

Dried plants were obtained from a local market in Manisa, Türkiye. Two to three pieces of the dried samples were taken and ground into powder in a porcelain mortar. A sample of 4 g was taken, and 40 mL of absolute ethanol was added. Extraction was carried out using Ultra-turrax (IKA T25, Staufen, Germany) at 5000×g for 3 minutes at room temperature for 30 minutes. The resulting extract solution was filtered and stored in amber glass bottles at +4 0C until further analysis.

2.2. Antioxidant Activity Assays

The antioxidant capacity of plant extracts was assessed using FRAP, DPPH, and ABTS assays with minor modifications (Benzie & Strain 1996; Brand-Williams et al. 1995; Arnao et al. 2001). In each assay, 150 µL of plant extract was mixed with 2850 µL of the respective reagent and incubated in the dark (30 minutes for FRAP; 2 h for DPPH and ABTS). Absorbance was measured at 593 nm (FRAP), 515 nm (DPPH), and 734 nm (ABTS) using a UV-Vis spectrophotometer (Jasco, Japan). Results were expressed as mM Trolox equivalents (TE) per gram of dry mass, based on linear standard curves (25–600 mM TE) [19-21].

2.3. Protein Quantification by the Warburg-Christian Method

Protein concentrations were determined using the Warburg-Christian method [22]. Absorbance values of plant extract solutions were measured at 260 nm and 280 nm in triplicate. The A280/A260 ratio was calculated for each sample (Jasco, Japan). Protein concentration (mg mL^{-1}) was then estimated using the following equation:
Protein concentration = (1.5 × A280) – (0.75 × A260) [22].

2.4. Quantification of Phenolic Compounds Using LC-MS/MS

The phenolic profiles of shoot extracts were determined using an Agilent 1260 Triple Quadrupole LC-MS/MS system. For separation, a C18 ODS HPLC column (25 x 4.6 mm, 5 µm) was employed. The injection volume for each sample was 2 µL. The mobile phase was composed of water with 0.1% formic acid (A) and 99.9% methanol (B). The gradient elution protocol was as follows: 2% B for 3 minutes, 25% B at 6 minutes, 50% B at 10 minutes, 95% B at 14 minutes, and back to 2% B at 17.5 minutes. The flow rate was set to 0.4 mL/min. Compound identification was carried out in both positive and negative ionization modes. In the LC-MS/MS analysis, calibration curves for standard solutions (Sigma Aldrich, USA) for phenolic compounds were constructed in the range of 25-1000 µg/L [23].

Statistical Analysis

Data were analyzed by two-way analysis of variance (ANOVA) using the GraphPad Prism 8.4.2 program. Means were separated from each other using Bonferroni's multiple comparison test ($p<0.05$). All analyzes were achieved in triplicate

3. RESULTS and DISCUSSION

In this study, the antioxidant potential and biochemical composition of Peganum harmala (üzerlik) were

evaluated using ethanol (ETOH) and water (AQUA) as extraction solvents. The analysis included antioxidant capacity assays (ABTS, DPPH, FRAP), total protein content, and quantification of individual phenolic compounds via chromatographic methods.

3.1. Antioxidant Activity Results

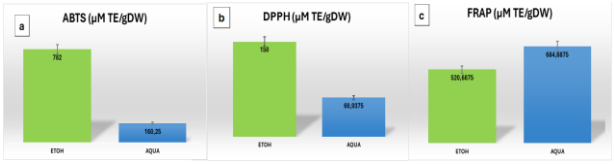


Figure 2: a: ABTS antioxidant activity results, b: DPPH antioxidant activity results, c: FRAB antioxidant activity results.

The ABTS assay revealed a significantly higher radical scavenging activity in the ethanol extract (782 µM TE/gDW) compared to the aqueous extract (160.25 µM TE/gDW). The DPPH results followed a similar trend, with ethanol extract showing 150 µM TE/gDW versus 60.94 µM TE/gDW in the aqueous extract. These results suggest that ethanol is more effective in extracting lipophilic antioxidant molecules. In line with our ABTS and DPPH data, Brand-Williams et al. (1995) demonstrated that ethanol extracts tend to show higher radical scavenging activity compared to aqueous extracts [20].

In contrast, the FRAP assay showed higher reducing power in the aqueous extract (684.69 µM TE/gDW) than in the ethanol extract (520.69 µM TE/gDW), suggesting that water may better extract hydrophilic antioxidants with strong reducing capacity. Regarding the FRAP results, Benzie and Strain (1996) noted that water-soluble antioxidants often exhibit stronger reducing power, supporting the higher FRAP values observed in the aqueous extract [19].

3.2. Protein Content Results

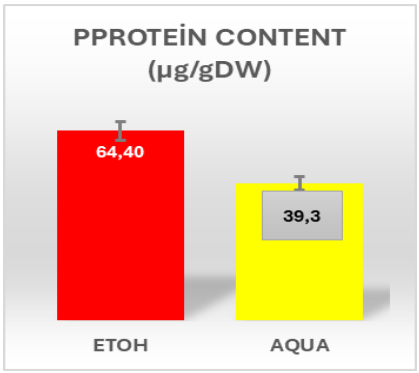


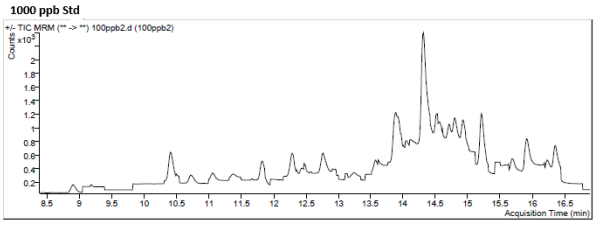
Figure 3: Protein contents of safflower.

Protein content was also higher in the ethanol extract (54.41 µg/gDW) compared to the aqueous extract (39.37 µg/gDW), further confirming ethanol's superior extraction efficiency for diverse bioactive compounds.

3.3. Phenolic Compound Results

Chromatographic analysis of phenolic acids and flavonoids provided deeper insight into the phytochemical differences between the two solvents: Aqueous extract was especially rich in 3-hydroxybenzoic acid (36.30 µg/g), 4-hydroxybenzoic acid (36.65 µg/g), ferulic acid (19.49 µg/g), and p-coumaric acid (9.18 µg/g), indicating that water is more efficient at extracting certain hydrophilic phenolic acids. Ethanol extract, while showing lower concentrations of these compounds, contained notable levels of chlorogenic acid (1.10 µg/g) and gallic acid (0.14 µg/g), which were absent in the aqueous extract. Interestingly, flavonoids such as hesperidin (0.0007 µg/g) and hyperoside (0.075 µg/g) were detected only in the aqueous extract. Resveratrol was present only in the ethanol extract (0.164 µg/g), consistent with its lipophilic nature.

Table 1. Total ion chromatograms of LC-MS/MS phenolic compounds.



Compound	Transition	RT	Resp.	Final Conc	Units
Gallic acid	168.9 -> 125.0	8.908	663	96.8167	ng/ml
3-hydroxytyrosol	153.0 -> 123.0	10.410	2143	96.3806	ng/ml
Protocatechuic acid	152.9 -> 108.9	10.734	733	105.7308	ng/ml
3,4-Dihydroxyphenylacetic acid	167.0 -> 123.0	11.065	533	98.4552	ng/ml
(+)-Catechin	289.0 -> 245.0	11.371	249	107.4714	ng/ml
Chlorogenic acid	355.0 -> 163.0	11.828	1549	101.0244	ng/ml
3-Hydroxybenzoic acid	137.0 -> 93.0	12.290	756	103.4128	ng/ml
4-Hydroxybenzoic acid	136.9 -> 93.1	12.292	1085	91.9430	ng/ml
(-)-Epicatechin	291.0 -> 139.1	12.453	414	87.9419	ng/ml
homovanillic acid	181.0 -> 137.1	12.709	49	71.2019	ng/ml
Caffeic acid	179.0 -> 135.0	12.769	1625	95.2782	ng/ml
Syringic acid	196.9 -> 181.9	12.866	49	90.0662	ng/ml
Vanillin	151.0 -> 136.0	13.249	388	89.1326	ng/ml
Verbascoside	623.0 -> 160.8	13.576	615	103.6418	ng/ml
Taxifolin	303.0 -> 285.1	13.880	2445	102.0455	ng/ml
p-Coumaric acid	162.9 -> 119.0	13.944	2168	99.4184	ng/ml
Sinapic acid	222.9 -> 207.9	13.981	225	100.3653	ng/ml
Ferulic acid	193.0 -> 134.0	14.058	376	97.2585	ng/ml
Luteolin 7-glucoside	447.1 -> 285.0	14.314	8151	102.3048	ng/ml
Hesperidin	611.1 -> 303.0	14.395	465	97.5013	ng/ml
Hyperoside	465.1 -> 303.1	14.530	1503	101.9126	ng/ml
Rosmarinic acid	359.0 -> 160.9	14.575	734	104.4581	ng/ml
Resveratol	226.9 -> 184.9	14.653	288	96.7263	ng/ml
oleuropein	539.2 -> 275.1	14.716	904	101.3095	ng/ml
Apigenin 7-glucoside	433.1 -> 271.0	14.807	1781	93.0727	ng/ml
Ellagic Acid	300.9 -> 283.6	14.962	10	46.0783	ng/ml
2-Hydroxycinnamic acid	162.9 -> 119.1	14.931	1568	99.7094	ng/ml
Pinoresinol	357.0 -> 151.0	15.087	45	107.0251	ng/ml
Eriodictyol	287.0 -> 151.0	15.215	2020	98.0744	ng/ml

Summary of Solvent Effects:

- Ethanol was superior in extracting total proteins, resveratrol, and certain phenolic acids like gallic and chlorogenic acid, contributing to higher ABTS and DPPH activity.
- Water extracted a wider range and higher quantity of hydrophilic phenolics, which may explain its stronger FRAP activity.

Table 2. Phenolic compound contents of samples of ethanol and water extracts.

Name	ETOH µg/g	AQUA µg/g
3-Hydroxybenzoic acid	3.402±0.02	36.302±0.5
4-Hydroxybenzoic acid	3.283±0.01	36.649±0.8
Caffeic acid	0.081±0.001	0.246±0.001
Chlorogenic acid	1.103±.0.001	-
Ferulic acid	3.727±0.02	19.486±0.6
Gallic acid	0.139±0.001	-
Hesperidin	-	0.0007±0.0
Hyperoside	-	0.075±0.0
p-Coumaric acid	0.818±0.001	9.182±0.8
Protocatechuic acid	0.483±0.001	1.386±0.001
Resveratol	0.164±0.001	
Syringic acid	0.707±0.001	3.311±0.01

The current findings are consistent with previous studies indicating that the choice of solvent significantly influences the extraction efficiency of bioactive compounds such as phenolic acids and proteins. For example, Singleton et al. (1999) **emphasized that the** Folin-Ciocalteu assay is sensitive to phenolic content, and solvents like ethanol often extract higher phenolic yields due to better solubility of semi-polar compounds [24]. The choice of solvent is a crucial determinant of both extraction yield and the composition of bioactive molecules such as phenolic compounds and proteins. Non-covalent interactions - including hydrogen bonding, hydrophobic interactions, and π- π stacking - largely govern how phenolics and proteins are released from plant matrices into the solvent. Ethanol and ethanol-water mixtures, being polar protic solvents, effectively interact with hydroxyl groups in phenolics, facilitating their solubilization and extraction. In addition, phenolics often form non-covalent complexes with proteins; thus, solvent systems capable of disrupting such interactions can promote the simultaneous extraction of both components. Consequently, the higher protein content in ethanolic extracts may reflect improved co-extraction due to these solvent-mediated interactions. Overall, solvent polarity and composition are key parameters that determine extraction efficiency, highlighting that solvent selection is a critical factor in obtaining comprehensive phytochemical profiles [24-27].

Specifically related to Peganum harmala, Shalaby and Hammouda (2014) reported the presence of diverse phenolic compounds and biological activities, aligning with our detection of compounds like 3-hydroxybenzoic acid, ferulic acid, and resveratrol [28]. Furthermore, Dai and Mumper (2010) reviewed extraction methods for plant phenolics, highlighting that ethanol is often more efficient than water in solubilizing a broad range of bioactive compounds [29]. Lastly, Zhou et al. (2016) emphasized the health benefits of phenolic compounds, especially in relation to compounds like resveratrol, which was detected in the ethanol extract in our study [30]. Antioxidants are substances that neutralize ROS and free radicals, thereby protecting cellular components, including lipids, proteins, and DNA, from oxidative damage [28-30]. In the present study, Peganum harmala seeds exhibited a remarkable antioxidant potential; ethanol extracts had higher ABTS and DPPH activities because of lipophilic antioxidants such as resveratrol, gallic acid, and chlorogenic acid, which are mainly responsible for the protection of lipid-rich cellular structures. The aqueous extracts were richer in hydrophilic phenolics, including 3-hydroxybenzoic, 4-hydroxybenzoic, ferulic, and p-coumaric acids, which are more potent in scavenging water-soluble ROS and enhancing the intracellular antioxidant defences. The complementary activities suggest that the seeds of P. harmala contain a wide spectrum of bioactive compounds that can mitigate oxidative stress, a pathophysiological phenomenon involved in the etiology of chronic disorders, including cardiovascular, neurodegenerative diseases, and cancer. The combined presence of both hydrophilic and lipophilic antioxidants in P. harmala supports its use as a natural source of functional ingredients for health promotion and disease prevention [31-34].

4. CONCLUSION

These results highlight the solvent-dependent selectivity in extracting bioactive compounds from Peganum harmala. Ethanol enhances extraction of lipophilic antioxidants and proteins, while water favors the extraction of hydrophilic phenolic acids and some flavonoids. The integration of antioxidant assays with protein and phenolic profiling provides a comprehensive evaluation of the extract's functional potential and bioactivity. Furthermore, the findings clearly demonstrate that the choice of solvent is a critical factor determining both the yield and chemical diversity of plant extracts. Solvent polarity and its ability to mediate non-covalent interactions directly influence the recovery of phenolic compounds and protein-bound antioxidants. Therefore, optimizing solvent systems not only improves extraction efficiency but also ensures a more accurate representation of the plant's true phytochemical profile. These insights underline the importance of solvent selection in developing standardized, high-quality natural extracts for use in pharmaceutical, nutraceutical, and functional food formulations.

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