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Antioxidant, Antimicrobial, and Antialzheimer Activities of *Tagetes patula* (Asteraceae)

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ABSTRACT

Plants are natural products used in the prevention and treatment of many diseases. In this study, antioxidant, antimicrobial, anticholinesterase activities and total phenolic and flavonoid contents of *Tagetes patula* L. samples collected from Iraq were determined. The aerial parts of the plant were extracted with ethanol in a soxhlet device. The antioxidant potential of the extracts was measured with Rel Assay kits. Antimicrobial activity was determined by the agar dilution method against standard bacterial and fungal strains. To determine anticholinesterase activity acetyl and butyrylcholinesterase inhibitions were tested. The total phenolic content of the samples was carried out using the Folin-Ciocalteu reagent. The quantification of flavonoids was conducted using an aluminum chloride assay. As a result of the analyses, the total antioxidant value of the plant extract was determined as 5.386±0.142 mmol Trolox equiv./L, the total oxidant value was 8.287±0.146 µmol H_2O_2 equiv./L and the oxidative stress index was determined as 0.154±0.003. Plant extracts showed the highest activity against *Candida* species. It was also effective against bacterial and fungal strains at concentrations between 50-400 µg/mL. Acetylcholinesterase activity of the plant extract was determined as 24.97±0.98, and butyrylcholinesterase activity was determined as 35.65±0.94. Additionally, its total phenolic content was determined as 63.64±0.74 mgGAE/g and its total flavonoid content was 108.9±1.55 mgQE/g. It has been determined that the plant has antioxidant, antimicrobial, and antiallergic potential.

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Tagetes patula'nın (Asteraceae) Antioksidan, Antimikrobiyal ve Antialzheimer aktiviteleri

ÖZET

Bitkiler birçok hastalığın önlenmesinde ve tedavisinde kullanılan doğal ürünlerdir. Bu çalışmada *Tagetes patula*'nın Irak'dan toplanan örneklerinin antioksidan, antimikrobiyal, antikolinesteraz aktiviteleri ve toplam fenolik ve flavonoid içerikleri belirlenmiştir. Bu kapsamda bitkinin toprak üstü kısmının etanol ile soxhlet cihazında özütleme işlemi yapıldı. Özütlerin antioksidan potansiyeli Rel Assay kitleri ile ölçüldü. Antimikrobiyal aktivite standart bakteri ve fungus suşlarına karşı agar dilüsyon metodu ile belirlendi. Antikolinesteraz aktivite için asetil ve bütirilkolinesteraz inhibisyonları test edildi. Numunelerin toplam fenolik içeriğinin miktarının belirlenmesi, Folin-Ciocalteu reaktifi kullanılarak gerçekleştirildi. Flavonoidlerin miktarının belirlenmesi, bir alüminyum klorür tahlili kullanılarak gerçekleştirildi. Yapılan analizler sonucunda bitki özütünün toplam antioksidan değeri 5.386±0.142 mmol Trolox equiv./L, toplam oksidan değeri 8.287±0.146 µmol H_2O_2 equiv./L ve oksidatif stress indeksi 0.154±0.003 olarak belirlendi. Bitki özütleri en yüksek aktiviteyi *Candida* türlerine karşı

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gösterdi. Ayrıca bakteri ve fungus suşlarına karşı 50-400 µg/mL arasındaki konsantrasyonlarda etkili olduğu tespit edildi. Bitki özütünün asetilkolinesteraz aktivitesi 24.97±0.98 µg/mL, bütirilkolinesteraz aktivitesi 35.65±0.94 µg/mL olarak belirlendi. Ayrıca toplam fenolik içeriği 63.64±0.74 mgGAE/g, toplam flavonoid içeriği 108.9±1.55 mgQE/g olarak tespit edildi. Bu kapsamda bitkinin antioksidan, antimikrobiyal ve Antialzheimer potansiyelinin olduğu tespit edilmiştir.

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INTRODUCTION

Traditional medicine has a very important place in human history. Different natural products are used in the fight against many diseases, based on old information (Çömlekçioğlu et al., 2022). The most commonly used among these natural products are plants. Many plants are used in different communities for many purposes such as burning, shelter, food, or medicine (Dogan et al., 2023). In many studies conducted on plants, it has been reported that plants have many activities such as antioxidant, anticancer, antiaging, anti-inflammatory, antiproliferative, hepatoprotective, antioxidant, antimicrobial, and DNA protective (Tutus et al., 2010; Mohammed et al., 2020a; Madani et al., 2022; Unal et al., 2022; Kalkan et al., 2023; Sevindik et al., 2023; Uysal et al., 2023). For this reason, determining the biological activities of plants is very important in terms of their usage potential. One of these plants is *T. patula*, which originates from America and is widespread around the World (Rueda et al., 2018). *Tagetes sp.* has demonstrated antibacterial, antifungal, and insecticidal activity in the control of many pests and diseases, especially in nematode management programs (Ismail et al., 2019; Gongalla, 2020).

It is an annual plant species of *T. patula* (Asteraceae) known as French marigold. It is easily grown with thousands of different varieties in bright shades of yellow and orange. It blooms from July to October. Its flowers are used to color foods (Romagnoli et al., 2005). *Tagetes* has approximately 30 species and is also used in traditional medicine in many regions of the world (Xu et al., 2012). The flowers and leaves of marigolds are used as folk medicine in the treatment of fever, liver diseases, diarrhea, vomiting, colic, and skin diseases (Kafaltiya et al., 2019). Plant extracts and essential oils are bioactive and potentially allelopathic against many pathogenic organisms such as bacteria, fungi, nematode viruses, acarid, and insects (Rueda et al., 2018). In this study, while determining the total phenolic content, total flavonoid content, and antimicrobial activity of the plant, we also aimed to determine the total antioxidant and total oxidant values and anticholinesterase activity of *T. patula* for the first time.

MATERIAL and METHOD

T. patula species were collected from Iraq (Erbil). Muddy and dusty aboveground parts of the plant were cleaned using distilled water. It was then ground into powder in a mechanical grinder. Then, thirty grams of the powder samples were weighed and extracted in a soxhlet apparatus. The extraction procedure was applied to 30 g of sample in 250 mL ethanol at 50˚C for 6 hours. Then, the solvents of the extracts were evaporated to obtain crude extract.

Antialzheimer tests

The anticholinesterase activity of the plant was determined for its potential anti-Alzheimer effect. For this, the Ellman method was used (Ellman et al., 1961). Galantamine was used as a standard. The plant extract was prepared at concentrations of 3.125-200 µg/mL. Then, 130 µL of 0.1 M pH=8 phosphate buffer, 10 µL of stock solution, and 20 µL of enzyme (AChE or BChE enzyme solution) were added to the microplate and incubated for 10 min at 25 °C in the dark. 20 µL of DTNB (5,5′-dithiobis-(2-nitrobenzoic acid)) solution and 20 µL of substrate (acetylcholine iodide or butyrylcholine iodide) were added. Reading was made with a spectrometer at a wavelength of 412 nm. The absorbance readings of the samples were repeated 3 times. IC_{50} values of percent inhibition of the samples was expressed as µg/mL (Kurt et al., 2020).

Inhibition (%) = [Acontrol – A sample / Acontrol] x100

Antimicrobial Activity Tests

Stock solutions were prepared from the plant extract at concentrations ranging from 125.5-800 µg/mL. From these extract concentrations, the lowest concentrations that prevented the growth of bacterial and fungal strains were determined. *Staphylococcus aureus* ATCC 29213, *S. aureus* MRSA ATCC 43300, *Enterococcus faecalis* ATCC 29212, *Escherichia coli*

ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Acinetobacter baumannii* ATCC 19606 were used as bacterial strains. *Candida albicans* ATCC 10231, *C. krusei* ATCC 34135 and *C. glabrata* ATCC 90030 were used as fungal strains. Bacteria were grown in Hinton Broth medium. The growth of fungi was carried out in RPMI 1640 Broth medium (Baba et al., 2020).

Total Phenolic and flavonoid Tests

A stock solution was prepared from the plant extract at a concentration of 1 mg/mL. After 250 mL of this solution was taken and mixed with 1 mL of Folin-Ciocalteu reagent (1:9, v/v), 0.75 mL of 1% Na_2CO_3 was added. Then incubated for 2 hours at room temperature and finally measured at 760 nm. According to the calibration curve of the gallic acid standard solution, the total phenolic content (TPC) was expressed as mgGAE/g (Bal et al., 2023).

The total flavonoid content (TFC) of the plant extract was analyzed by aluminium chloride assay. 0.1 mL 10% Al $(NO_3)_3$, 0.1 mL 1 M NH_4CH_3COO, 4.3 mL methanol, 0.5 mL quercetin and 0.5 mL plant extracts were mixed. It was then incubated for 40 minutes, and absorbance was measured at 415 nm. According to the calibration curve of the quercetin standard solution, the total flavonoid content (TFC) was expressed as mgQE/g (Korkmaz et al., 2023).

Total antioxidant and oxidant analyze

Rel Assay kits were used to determine the antioxidant potential of the plant extract. Trolox was used as a calibrator in the total antioxidant (TAS) test, and hydrogen peroxide was used as a calibrator in the total oxidant (TOS) test. TAS values were expressed as mmol Trolox equiv./L. TOS values were expressed as µmol H_2O_2 equiv./L (Erel, 2004; Erel 2005). OSI (oxidative stress index) value was determined by dividing TOS values to TAS values and taking their percentages (Sevindik, 2019).

RESULTS AND DISCUSSION

Anticholinesterase activity

Alzheimer's is the most common neurodegenerative disease. The number of cases, which has been increasing in recent years, is expected to increase further in the coming years. Due to the increasing age scale, approximately 5 million new cases are seen every year around the world. On the other hand, the pathogenesis of the disease is still not fully known (Konrath et al., 2013). However, the most common treatment options include inhibition of cholinesterases. In this study, the anti-AChE and anti-BChE potentials of the ethanol extract of *T. patula* were determined. The obtained IC_{50} values are shown in Table 1.

Table 1 Anti-AChE and anti-BChE values of *T. patula*
Çizelge 1. T. patula'nın anti-AChE ve anti-BChE değerleri

Exctract and Control	AChE µg/mL	BChE µg/mL
Ethanol extract	24.97±0.98	35.65±0.94
Galantamine	9.46±0.18	15.86±0.41

In the literature, the AChE inhibition values of the ethanol extract of *T. patula* were reported to be 22.37-25.33 µ mol/mg (Ramakrishnan et al., 2015). In this study, anti-AChE and anti-BChE potentials were determined using the ethanol extract of *T. patula*. Additionally, galantamine was used as a standard. It was determined that *T. patula* used in this study showed lower activity than galantamine. It is very important to determine the presence of enzymes that cause the etiology of diseases. In addition, inhibition of these enzymes can make important contributions to the treatment of diseases (Świątek et al., 2021). It appears that *T. patula* used in this study has acetyl and butyrylcholinesterase inhibition potential. These findings suggest that *T. patula* may be a natural source for the treatment of neurodegenerative diseases.

Antimicrobial activity

Today, microorganisms are at the root of many diseases. The effects of antimicrobial drugs used against microorganisms in the market are insufficient (Eraslan et al., 2021). Among the general reasons for this is the increase in the number of resistant microorganisms due to unconscious use of antibiotics. The researchers have turned to the discovery of new antimicrobial drugs. Possible side effects of synthetic drugs have led researchers to natural antimicrobial sources (Bal et al., 2022; Lomberg et al., 2023; Mohammed et al., 2023). In this study, the antimicrobial potential of the ethanol extract of *T. patula* was determined. The findings obtained are shown in Table 2.

Table 2 MIC values of ethanol extract of *T. patula*
Çizelge 2. T. patula'nın etanol ektraktının MIC değerleri

	S. aureus	*S. aureus* MRSA	*E. faecalis*	*E. coli*	*P. aeruginosa*	*A. baumannii*	*C. albicans*	*C. glabrata*	*C. krusei*
Ethanol	200	200	100	400	400	200	50	50	50

*****50, 100, 200, 400 µg/mL represents the lowest concentration that inhibits the growth of microorganisms.

In this study, it was determined that the ethanol extract of *T. patula* was effective against standard bacterial and fungal strains at concentrations between 50-400 µg/mL. It has previously been reported that methanol extract of *T. patula* is effective against *Bacillus subtilis*, *Enterococcus faecalis* and *Staphylococcus aureus* (Latifian et al., 2021). In a different study, it was reported that different parts of *T. patula* were effective against *Bacillus cereus*, *Bacillus subtilis*, *Listeria monocytogenes*, *Micrococcus luteus*, *Micrococcus lysodeikticus*, *Mycobacterium fortuitum*, *Staphylococcus aureus*, *Staphylococcus aureus* AB, *Staphylococcus saprophyticus*, *Streptococcus faecalis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella paratyphi*, *Salmonella typhi* and *Shigella flexneri* (Faizi et al., 2008). In another study, it was reported that different parts of *T. patula* have antimicrobial activities against *Serratia fonticola*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Proteus mirabilis*, *Escherichia coli*, *Staphylococcus aureus*, *S. epidermidis*, *S. saprophyticus*, *Streptococcus agalactiae*, and *Streptococcus oralis* (Safar et al., 2020). In this study, it was determined that *T. patula* was effective against standard bacterial and fungal strains using ethanol extract. It was observed that the plant extract exhibited the highest activity against *C. albicans*, *C. glabrata,* and *C. krusei* at a concentration of 50 µg/mL. It later became effective against *E. faecalis* at a concentration of 100 µg/mL. Subsequently, it was effective against *S. aureus*, *S. aureus* MRSA, and *A. baumannii* at a concentration of 200 µg/mL. It also showed activity against *E. coli* and *P. aeruginosa* at a concentration of 400 µg/mL. Latifian et al. (2021) found in their study that the ethanolic extract of *T. patula* showed good antibacterial effects against human pathogens. Rueda et al. (2018) examined the effect of methanolic flower extract and essential oil of *T. patula* on *R. solanacearum* bacteria and determined that the bacteria were highly sensitive to both components at a concentration of 100 mg/mL. In line with literature data and this study data, it has been observed that *T. patula* has antimicrobial potential.

Total phenolic and total flavonoid contents

As a result of their defense systems, plants produce secondary metabolites that are not nutritional but medically important (Türkmen and Koçer, 2021). In this study, total phenolic and total flavonoid contents of *T. patula* were determined. The findings obtained are shown in Table 3.

It is thought that the phenolic compound contents in plants, including flavonoids, have the ability to eliminate free radicals (Rueda et al., 2018). In the literature, it has been reported that the total phenolic contents of the flower and leaf parts of *T. patula* are 30 and 80 mg/g, and the total flavonoid content is 30 and 65 mg/g (Kushwaha and Verma, 2017). While the total phenolic contents of *T. patula* used in this study were similar compared to this study, the total flavonoid contents were determined to be higher. Tiwari et al. (2023) determined the total flavonoid content of the ethanolic extract of *T. patula* flower as 119.08 mg/g and the total flavonoid content as 71 mg/g. When we compared this study with Tiwari et al. (2023) study, we found that phenolic values were lower and flavinoid values were higher. In a different study, the total phenolic contents of the flower and leaf parts of *T. patula* were reported as 11.54-103.70 mg/g (Salachna et al., 2021). Rueda et al. (2018) determined the total phenolic content in the methanol extract of the leaves and flowers of *T. patula* as 227.67 mg/g and 153.48 mg/g, respectively. In another study, the total phenolic content of different fractions of *T. patula* was reported as 14.85-67.44 mg/g (Kuddus et al., 2012). Compared to these studies, the total phenolic contents of the aboveground parts of *T. patula* used in this study are similar, although there are some differences. It is thought that this difference arises from the difference in soil structure in the regions where the plants are collected and the variability of the stress conditions they encounter.

Table 3 TPC and TFC values of *T. patula*
Çizelge 3. T. patula'nın TPC ve TFC değerleri

	TPC (mgGAE/g)	TFC (mgQE/g)
Ethanol extract	63.64±0.74	108.9±1.55

Values are given as mean ± standard deviation. (n=3)

Antioxidant activity

Oxidant compounds are unstable compounds produced in routine metabolic processes. Oxidant compounds play a role at low doses in defending against infections or promoting the death of cancer cells (Bal et al., 2019). But as levels of oxidant compounds increase, they can become membrane bound. Antioxidants protect living organisms from diseases by reducing or suppressing the effects of oxidant compounds in living organisms (Krupodorova and Sevindik, 2020; Mushtaq et al., 2020). However, if the balance between oxidant compounds and the antioxidant defense system shifts towards oxidant compounds, oxidative stress occurs. As a result of oxidative stress, diseases such as degenerative diseases (Parkinson, Alzheimer's, AMD), rheumatic, pulmonary, digestive, cardiovascular, metabolic progressive chronic diseases, and cancer are linked to oxidative stress. They can promote chronic diseases such as cataracts, cancer, coronary heart disease, diabetes, and kidney failure (Manda et al., 2009; Sevindik et al., 2018; Gürgen et al., 2020). Supplemental antioxidants may serve to reduce the

possible effects of oxidative stress (Hawas et al., 2013). Plants are very important natural products in terms of their supplementary antioxidant potential. In this study, the antioxidant potential of *T. patula* was determined. The findings obtained are shown in Table 4.

Table 4 TAS, TOS and OSI values of *T. patula*
Çizelge 4. T. patula'nın TAS, TOS ve OSI değerleri

	TAS (mmol Trolox equiv./L)	TOS (µmol H_2O_2 equiv./L)	OSI (TOS/TASx10)
Ethanol extract	5.386±0.142	8.287±0.146	0.154±0.003

Values are given as mean ± standard deviation. (n=3)

Many previous studies have reported the antioxidant potential of *T. patula* using different methods (Negi et al., 2013; Munhoz et al., 2014; Kashif et al., 2015; Riaz et al., 2020). In this study, the antioxidant potential of *T. patula* was determined for the first time using TAS and TOS kits. There are studies on different plant species using TAS and TOS kits. In these studies, TAS values of *Mentha longifolia* ssp. *longifolia*, *Allium calocephalum*, *Helianthemum salicifolium*, *Silybum marianum*, *Ferulago platycarpa*, *Galium aparine,* and *Glycyrrhiza glabra* were reported as 3.628, 5.853, 9.490, 5.767, 5.688, 5.147 and 8.770, respectively. TOS values were reported as 4.046, 16.288, 14.389, 12.144, 15.552, 18.679 and 14.590, respectively. OSI values have been reported as 0.112, 0.278, 0.157, 0.211, 0.273, 0.346 and 0.167, respectively (Sevindik et al., 2017; Mohammed et al., 2019a; Mohammed et al., 2019b; Mohammed et al., 2020b; Korkmaz et al., 2021; Mohammed et al., 2021a; Mohammed et al., 2021b). Compared to these studies, the TAS value of *T. patula* used in this study was found to be higher than *Mentha longifolia* ssp. *longifolia* and *Galium aparine*, and lower than *Allium calocephalum*, *Helianthemum salicifolium*, *Silybum marianum*, *Ferulago platycarpa,* and *Glycyrrhiza glabra*. TAS value is an indicator of the totality of antioxidant compounds found in natural products (Selamoglu et al., 2020). In this context, it appears that *T. patula* used in this study has antioxidant potential. TOS value is an indicator of the oxidant-active compounds produced within natural products. The OSI value shows the percentage of oxidant compounds suppressed by antioxidant compounds. High OSI value shows that natural products are insufficient to suppress oxidant compounds. (Selamoglu et al., 2020). It was observed that the TOS and OSI values of *T. patula* used in this study were higher than *Mentha longifolia* ssp. *longifolia* and lower than *Allium calocephalum*, *Helianthemum salicifolium*, *Silybum marianum*, *Ferulago platycarpa*, *Galium aparine* and *Glycyrrhiza glabra*. In this context, it was observed that *T. patula* used in this study produced fewer oxidant compounds due to environmental effects. In addition, it appears that the antioxidant defense system functions well in suppressing oxidant compounds. In this context, it is thought that *T. patula* may be a natural antioxidant source.

CONCLUSION

In this study, the biological activities of *T. patula*, which is an easy-to-cultivate, fast-growing, and widespread species, were determined. Antioxidant, antimicrobial, and anticholinesterase activities, as well as total phenolic and flavonoid contents of *T. patula* were determined. As a result of the analyses, it is thought that the ethanol extract of the plant can be used both as a food preservative and against human pathogenic microorganisms due to its high antioxidant and antimicrobial potential. It is also thought that the plant may support the treatment of neurodegenerative diseases due to its antioxidant and anticholinesterase potential. Although the findings are compatible with the *T. patula* data used in folk medicine studies, the positive properties of this plant on living things can be detailed in different studies.

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Contribution Rate Statement Summary of Researchers

The authors declare that they have contributed equally to the article.

Conflict of Interest

The authors of the article declare that there is no conflict of interest between them.

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