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Original Article

Assessment of antioxidant and neuroprotective activity of plants from the Lamiaceae family

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ABSTRACT

Background and Aims: Plants from the Lamiaceae family are shown to have pharmacological activities, including anti-inflammatory, antidiabetic, antiasthmatic, hypolipidemic, antibacterial. This research measured the antioxidant and neuroprotective capacity of methanol extracts from the *Marrubium vulgare* L., *Phlomis armeniaca* Willd., *Thymus haussknechtii* Velen. and, *Thymus kotschyanus* Boiss. & Hohen plants in cellular and cell-free systems.

Methods: The neuroprotective potential of *Marrubium vulgare, Phlomis armeniaca, Thymus haussknechtii*, and *T. kotschyanus* were determined against H_2O_2 toxicity in SH-SY5Y, the human neuroblastoma cell line. The antioxidant capacity of methanol extracts was examined by radical scavenging assays using static exempt chemical groups, 2.2'-diphenyl-1-picrylhydrazyl-hydrate (DPPH) and 2.2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS). Folin-Ciocalteau and Aluminum chloride assays were used to measure phenolic and flavonoid contents of the extracts.

Results: Following these experiments, the effect of three different concentrations of extracts (1, 10 and 100 µg/mL) on cell viability was assessed by a WST-1 [2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium)]. The methanol extract of *Marrubium vulgare* was found to have the highest antiradical activity against DPPH (76.439±0.42%). The *Thymus kotschyanus* (10µg/mL) protected cells from H_2O_2-induced toxicity in all the extracts ($p<0.05$).

Conclusion: In our report, we suggest that *Thymus kotschyanus* have potential neuroprotective activity because of the existence of polyphenolic compounds, flavonoids, and phenolic acids.

Keywords: Antioxidant activity, Lamiaceae, Neuroprotective, Oxidative stress

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurological disorder with a prevalence of 5% among individuals over 65 years old, increasing to 30% among those over 85 years old. It is the most common form of dementia, as well as the most prevalent neurodegenerative disorder, and dramatically affects cognitive and behavioral skills. One of the contributing factors in AD's progression is the presence of oxidative stress, a disturbance in the balance between oxidants and antioxidants, in favor of the oxidants (Ververis et al., 2020). Antioxidants are the key players combating oxidative stress in diseases. Several studies have shown the high antioxidant capacity of plant species which are efficient in cell development, adjusting membrane potential, or inhibiting lipid peroxidation (El Houri, & Rosado, 2019; Silva et al., 2019; Poznyak et al., 2020). These studies correlated with the secondary metabolites of plants such as lipo- and water-soluble nutrients and polyphenols (Ginsburg, Kohen & Koren, 2011). The drugs obtained from medicinal plant materials from members of the family Lamiaceae have a neurotropic effect, enhance the affinity of gamma-aminobutyric acid (GABA) for GABA-receptors in the subcortical formations, primarily in the reticular formation, weakening its stimulating effect on the cerebral cortex. Flavonoids, triterpenic acids (ursolic and oleanolic), phenylpropanoids (rosmarinic and caffeic acids), terpenoids and aromatic compounds which are components of the essential oil (linalool, linalyl acetate, thymol, carvacrol, etc.), alkaloids, alkaloid-like compounds and iridoids, are often studied in this context (Zvezdina et al., 2020).

The Lamiaceae (Labiatae) family is represented by 258 gen-

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era and around 7886 species in the world (Abdelhalima & Hanrahan, 2021). The family has 48 genera and 782 taxa (603 species, 179 subspecies and varieties), 346 taxa (271 species, 75 subspecies and varieties) of which 44% are endemic in Turkiye (Celep, & Dirmenci, 2017). Many plant taxa of this family are used as culinary herbs, sources of aroma and in traditional medicine (Selvi, Polat, Çakılcıoğlu, & Celep, 2022). Members of the Lamiaceae family gained importance in areas such as medicine, food, cosmetics, and perfumery (Ozturk, 2015).

In Turkiye the genus *Marrubium* L. is represented by 34 taxa of which 17 are endemic with an endemism rate of 50% (Deshmukh, Reddy, & Shende, 2022). Recent studies demonstrated that *M. vulgare* offered different *in vivo* and *in vitro* pharmacological activities, including antihypertensive, anti-inflammatory, antidiabetic, vasodilator, antiasthmatic, hypolipidemic, antibacterial, and antifungal (Aćimović et al., 2020; Gavaric et al., 2022; Akbulut, Kose, Demirci, & Baykan, 2023). More than 54 secondary metabolites were identified from *M. vulgare*. The secondary metabolites of diterpenes, sesquiterpenes, flavonoids, and phenylpropanoids were isolated from various parts of *M. vulgare* (Aćimović et al., 2020). Marrubiin, marrubiinic acid, and marrubenol were the most abundant diterpenes that displayed pain-relieving and edema-relieving activities. Arenarioside, acteoside, forsythoside B, and ballotetroside are phenylpropanoids that have strong antitumor and anti-inflammatory activities (Lodhi, Vadnere, Sharma, & Usman, 2017).

Phlomis armeniaca Willd., known as 'boz şavlak' in Turkiye, is a medicinal plant of Lamiaceae family. The aerial parts of this plant are used as tea in traditional medicine for cold and gastrointestinal problems, including digestion disorders, ulcers, and stomachache (Uysal, Gunes, Sarikurkcu, Celik, Durak, & Uren, 2016). A few studies with the aerial parts of *P. armeniaca* demonstrated that the plant has iridoids, phenylethanoid glycosides, lignans, phenylpropanoids, monoterpenes, and diterpenoids as major compounds. The antinociceptive, antiulcerogenic, anti-inflammatory, antiallergenic, anticancer, and antimicrobial activities are reported for some species of *Phlomis* (Aybey, 2020; Sarıkurkcu & Zeljkovic, 2020; Tarhan, Urek, Öner, Nakipoglu, 2022; Kunter, et al., 2023).

Thymus L. in the Lamiaceae family is represented by 39 species and 59 taxa in Turkiye and the proportion of endemism for this genus is greater than 50%. *Thymus haussknechtii* is another endemic plant in Turkiye and in conventional remedies, this species is utilized for its antibacterial, antifungal, antihelminthic, antispasmodic, sedative, antioxidant, and diaphoretic activities (Ozturk, 2015; Yigitkan et al., 2022).

In this study, the primary goal was to determine the neuroprotective potential of *Marrubium vulgare, Phlomis armeniaca, Thymus haussknechtii* and *T. kotschyanus* against H_2O_2-induced apoptosis. Additionally, radical scavenging assays were performed to confirm their antioxidant activities.

MATERIALS AND METHODS

Chemicals

Folin Ciocalteu reagent and methanol were purchased from Merck (Germany). Sodium hydroxide, 2.2'-diphenyl-1-picrylhydrazyl, α-tocopherol, aluminum chloride, and gallic acid were obtained from Sigma Chemical (Sigma-Aldrich Gmbh, Germany). SH-SY5Y, the human neuroblastoma cell line, was purchased from the American Type Culture Collection (ATCC, Cat. No. CRL-2266). Dulbecco's Modified Eagle Medium (DMEM) and fetal bovine serum (FBS) were provided by Life Technologies (Grand Island, NY). The WST-1 [2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium)] was acquired from Takara Bio USA (Mountain View, CA, USA). An analytical grade of other synthetic compounds and solvents were used.

Plant materials and extraction

The aerial parts of *M. vulgare, P. armeniaca, T. haussknechtii* and *T. kotschyanus* (Lamiaceae) were collected in June 2018 from Elazig, Turkiye. The identification of plants was made by Ugur Cakilcioglu, from Tunceli University. The voucher specimens (herbarium numbers: 1635 for *M. vulgare*, 1636 for *P. armeniaca*, 1637 for *T. haussknechtii*, and 1638 for *T. kotschyanus*) were saved in the herbarium of the Faculty of Pharmacy, Ege University, Izmir, Turkiye. *M. vulgare, P. armeniaca, T. haussknechtii* and *T. kotschyanus* were entitled as MV, PA, TH, and TK, separately. The collected plant materials were air-dried at room temperature. The powdered samples (40g) were extracted with 400mL methanol using a Soxhlet type extractor at 60°C for six hours. After the solvent was filtered by Whatman No. 1 filter paper, extracts were dissipated by a rotating evaporator under low pressure. Extracts were kept at + 4°C in the dark until use. The percentage yield of methanol extracts of MV, PA, TH and TK were found as 8.25%, 11.60%, 7.42%, and 8.84%, respectively.

Cell culture studies

The cells were suspended in DMEM with the addition of 10% FBS, 1% penicillin, and streptomycin. For the WST-1 assay, cells were transferred to 96-well plates at a density of 2×10^3 cells/well. Stock solutions of the extracts were prepared in sterile DMSO (dimethyl sulfoxide). The final concentration of DMSO was kept lower than 0.1% in cells.

Cell viability assay

The 96-well plates of seeded cells were incubated for 24 hours. Following the 24 hour incubation period, the cells were treated with three concentrations of extracts (1, 10, and 100µg/mL) for two hours. Then, cells were cleaned twice with sterile

phosphate-buffered saline (PBS) and treated with 250mM H_2O_2 in sterile Ca^{2+} and Mg^{2+} -added PBS for 60 minutes. The H_2O_2 in the well was replaced with a warm medium after one hour and incubated for an additional 17 hours. Cell proliferation after 18 hours was determined by the WST-1 assay as described previously (Loubidi et al., 2016).

Antioxidant activity assays

DPPH radical scavenging assay

The DPPH (2.2'-diphenyl-1-picrylhydrazyl) radical scavenging activity of methanol extracts was assessed by the method described by Fukumoto and Mazza (Fukumoto & Mazza, 2000). 1000µL of 1mg/mL methanol extracts were appended to 4mL of 0.004% DPPH in methanol. The absorbance was assessed following 30 minutes at 517nm. The percentage inhibition of free radicals was calculated as follows:

$$\%Inhibition = [(A_c - A_s)/A_b] \times 100$$

(A_c: the absorbance of the control, As: the absorbance of the sample).

ABTS radical scavenging assay

The ABTS solution was arranged and diluted with ethanol until it gave a 0.750 absorbance in 734nm by the ABTS assay (Re et al., 1999). A 0.1mL of concentrates and 10µL α-tocopherol were appended to 1mL ABTS+ solution, and an absorbance change was seen in 734nm during the six minutes. The α-tocopherol was utilized as a standard solution. The ABTS % inhibition was determined as follows:

$$ABTS\%inhibition = (Abs_1 - Abs_2)/Abs_1 \times 100.$$

(Abs_1: the initial absorbance, Abs_2 : the absorbance at 6 min).

Determination of total phenol and flavonoid contents

As indicated by the method for Folin-Ciocalteu, the total phenol content of 0.1mL concentrates were added to 2.8mL deionized water. A 2mL 2% sodium carbonate and 0.1mL of 0.1 N Folin–Ciocalteu reagent was included in this solution. After standing for 30 minutes at room temperature, the absorbance of the solution was assessed at 750nm on an UV/Vis spectrophotometer (Unicam 8625). A standard solution of gallic acid solution was utilized (Chang, Yang, Wen, & Chern, 2002). Subsequently, the results were shown as mg gallic acid equivalents.

The aluminum chloride assay was utilized to determine the total flavonoid content (Woisky & Salatino, 1998). According to this method, 1.5mL of ethanol, 0.1mL of 10% aluminum chloride, and 2.8mL of purified water were added to the 0.5mL extracts. The mixture solution stayed at room temperature for 30 minutes, and the absorbance was assessed at 415nm on the UV/Vis spectrophotometer. As a standard solution of quercetin was utilized.

Statistical Analysis

The antioxidant capacity experiments were executed in triplicate. The data was presented as ± S.D. The comparison between groups was executed by a one-way analysis of variance (ANOVA). The P values of less than 0.05 were considered significant.

RESULTS

The antioxidant activities and measurements of the total phenolic and flavonoid contents of *M. vulgare, P. armeniaca, T. haussknectii*, and *T. kotschyanus* are shown in Table 1. The most active plant found for its antioxidant capacity and measure of total phenolic and flavonoids with activity assays was *T. kotschyanus*. For defensive impact against oxidative stress on a neuroblastoma cell line (SH-SY5Y) the most effective plant was the *T. kotschyanus.*

The total phenolic content in the taxa extended from 53.02 to 408.31mg gallic acid equivalent/100g, and the complete flavonoid content went from 41.98 to 138.62 to mg quercetin equivalent/100g, being most noteworthy for *T. kotschyanus* and least for *M. vulgare*. The most noteworthy DPPH radical scavenging activity (76.439%) was resolved for *M. vulgare*; the most noteworthy ABTS radical scavenging activity (54.867%) values were resolved for *T. kotschyanus*, while *T. haussknectii* and *M. vulgare* displayed the most reduced DPPH (28.417%) and ABTS (3.438%) values.

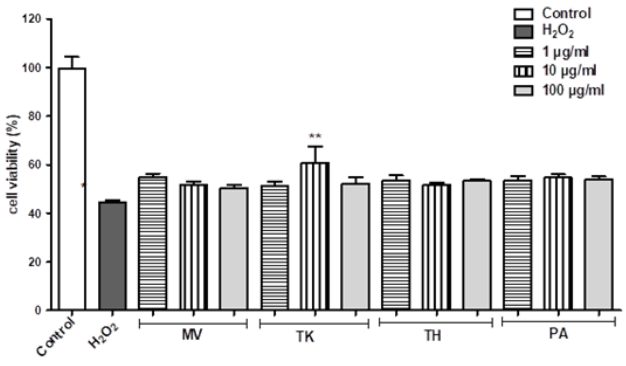

Figure 1. Cell viability analysis following methanol extract treatments are shown against H_2O_2-induced toxicity. The cells were pre-treated with various concentrations (1, 10 and 100µg/mL) of methanol extracts of MV (*Marrubium vulgare),* TK (*Thymus kotschyanus*), TH (*Thymus haussknectii*) and PA (*Phlomis armeniaca*) for two hours and exposed to H_2O_2 for one hour. Cell viability was measured by the WST-1 assay. All values are means ± SDs (n = 5),*p≤0.05 vs. untreated cells, **p≤0.05 vs. H_2O_2-treated cells.

Table 1. Antioxidant activities, total phenolic and flavonoid contents of *M. vulgare, P. armeniaca, T. haussknechtii* and *T. kotschyanus*

Plant name	DPPH (inhibition %)	ABTS (inhibition %)	TPC (mgGAE/100 g)[a]	TFC (mgQE/100 g)[b]
Marrubium vulgare	76.439±1.05[c]	3.438±4.02	53.02±2.66	41.98±3.84
Phlomis armeniaca	52.487±1.28	36.204±1.28	38.49±1.86	28.06±1.96
Thymus haussknectii	28.417±3.84	16.328±2.84	28.36±0.58	19.42±2.08
Thymus kotschyanus	36.246±2.56	54.867±4.06	408.31±1.08	138.62±4.06

[a] Total phenolic content expressed as gallic acid equivalents (mg gallic acid equivalent /100 g extract); [b] total flavonoid content expressed as quercetin equivalents (mg quercetin equivalent /100 g extract);
[c] results are mean ± SD of three replicate analysis; TEAC (trolox equivalent antioxidant capacity).

The investigation of cell viability following methanol extract treatments against H_2O_2-induced toxicity on neuroblastoma cell line appear in Figure 1. The expected protective effects of extracts were assessed in the H_2O_2-induced oxidative stress model. The adjustments in cell viability were resolved after exposure to determine the impact of concentrations on cell proliferation rate. Treatment with concentrations for 24 hours showed roughly a similar proliferation rate with control cells but it was not decided as cytotoxic and did not adjust the expansion of cells. The SH-SY5Y cells were pre-treated with extracts changing from 1 to 100µg/mL for two hours, after treatment with 250µM H_2O_2 for one hour. WST-1 measurements were used for to decide the cell viability. Figure 1 demonstrates that every chosen concentration figured out how to expand cell viability against H_2O_2. TK at 10µg/mL significantly decreased the H_2O_2-induced neuronal death, as it appeared with the expansion of cell viability ($p < 0.05$). The cell viability in the H_2O_2 group was discovered to be 44.21% ± 1.80 ($p < 0.05$), and the TK at 10µg/mL displayed at 36.40% neuroprotection against H_2O_2-induced toxicity.

DISCUSSION

A positive correlation between the contents of total flavonoid and total phenols and antioxidant activities of the plants was observed. Typical phenols that own antioxidant activity are recognized as flavonoids and phenolic acids (Meyre-Silva & Cechinel-Filho, 2010; Silva et al., 2019). The TPC of the extracts of *M. vulgare* and *T. haussknectii* were resolved as 19.08 and 320.96 mg/g gallic acid equivalents. The TFC of the concentrates of *M. vulgare* and *T. haussknectii* were acquired as 7.08 and 86.02 mg/g quercetin equivalents, respectively. Numerous flavonoids were isolated from *M. vulgare* and T. haussknectii. There were a few studies on antioxidant activities of*M. vulgare, P. armeniaca, T. haussknectii* and *T. kotschyanus* (Amri et al., 2017; Tohidi, Rahimmalek, & Arzani, 2017; Boroomand, Sadat-Hosseini, Moghbeli, & Farajpour, 2018). Furthermore, there were studies about defensive effects on cell cultures for these plants (Brahmi et al., 2015; Dibas, Yaghi, Mansi, Mhaidat, & Al-Abrounie, 2017). The utilized cell culture systems were not quite the same as in this work. Consequently, we needed to compare our outcomes with previous investigations.

Lamiaceae species are rich in phenolic acids contribute to neuroprotective activity (Dastmalchi, Dorman, Viorela, & Hiltunen, 2007). Polar extracts of *Thymus* species are used in the food, cosmetics, and pharmaceutical industry due to their protective activities (Afonso, Pereira, Neto, Silva, & Cardoso, 2017). Dietary antioxidant intake, such as for terpenes, and phenolic compounds, act as free radical scavenging molecules (Uttara, Singh, Zamboni, & Mahajan, 2009). In previous studies, volatile terpenoids and polyphenolic compounds were isolated from the *Thymus* species. Polyphenolic compounds from *Thymus* plants, predominantly flavonoids and phenolic acids, were published. The most common structure among flavonoids is found to be flavones (luteolin, apigenin and scutellarin) and flavanones (eriodictyol and naringin). The phenolic acids isolated from different *Thymus* species are caffeic acid and rosmarinic acid (Jordan, Martinez, Martinez, Monino, & Sotomayor, 2009). Oxidative damage caused by free radical interaction with neural cells leads to degeneration, while exogenous and endogenous antioxidants such as polyphenols, and flavonoids could retard cell death (Hassan, Ibrahim, Yusuf, Ahmad, & Ahmad, 2021). The neuroprotective activity of luteolin was observed against hydrogen peroxide-induced toxicity in primary neuronal cells.

CONCLUSION

Flavonoids apigenin and luteolin were found to exhibit neuroprotective effects against KCl-induced-Ca2+ overload and oxidative stress, beyond acting as acetylcholinesterase inhibitors (Cavallaro, Baier, Murray, Estevez-Braun, & Murray, 2018). We claimed the neuroprotection of *Thymus kotschyanus* was because of the existence of polyphenolic compounds, flavonoids, and phenolic acids. New research is required for the isolation of components responsible for biological activities and to clarify their structures.

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