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Can *Acanthus spinosus* be used as an alternative antioxidant and enzyme inhibitory agent?

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ABSTRACT

Plant polyphenols attract researchers because of their bioactive properties. In this study, the chemical compositions and *in vitro* antioxidant and enzyme inhibitory activities of ethyl acetate (EtOAc), methanol (MeOH), and water extracts obtained from the aerial parts of *Acanthus spinosus* L. were investigated. The MeOH extract was found to be rich in phenolics and flavonoids (47.4 mg GAE/g and 19.2 mg RE/g, respectively). Verbascoside (28979 μg/g), vanillic acid (4342 μg/g), pinoresinol (3211 μg/g), syringic acid (1272 μg/g), and kaempferol (1170 μg/g) were detected as the main components of MeOH extract in chromatographic analyzes. While MeOH extract showed high activity in DPPH radical scavenging, CUPRAC and FRAP tests (44.1, 106, and 60.8 mg TE/g, respectively), chelating effect and phosphomolybdenum tests resulted in the superiority of EtOAc extract (18.6 mg EDTAE/g and 473 mg TE/g, respectively). The EtOAc extract exhibited notable activities in the butyrylcholinesterase (BChE), α-amylase, and α glucosidase inhibitory activity tests (1.9 GALAE/g, 785 and 1658 mg ACE/g, respectively). It has been concluded that *A. spinosus* extracts are an alternative source of phytochemicals in the food, cosmetic and medical industries due to their remarkable antioxidant and enzyme inhibitory activities.

1. Introduction

Plant polyphenols are biologically active molecules that are naturally synthesized by plants belonging to various families and carry hydroxyl groups attached to aromatic rings in their structures (Zhou et al., 2019). It is possible to consider plant polyphenols in two basic categories, flavonoids and non-flavonoids, for ease of classification. Flavonoids are divided into various subgroups such as flavones, flavonols, chalcones, anthocyanidins, flavonols, flavanones. Among the non-flavonoid polyphenols, there are phenolic acids, saponins, stilbenes, tannins, etc. (Zhou et al., 2019). Researchers suggest that many of these bioactive molecules are highly capable of antioxidant activity. Therefore, there is a consensus that the damage due to oxidative molecules is reduced in people-fed diets rich in polyphenols (Boo, 2019; Pawlowska et al., 2019).

Alzheimer's is a disease that affects many people around the world. Many interrelated proteins play a critical role in the pathogenesis of this disease. During the disease, cognitive skills weaken depending on the decrease of cortical and hippocampal acetylcholine (ACh) and butyrylcholine (BCh) levels in the brain (Melnikova, 2007). ACh and BCh reduction in the brain due to cholinesterase (ChE) activity usually begins to appear after the age of 60. Researchers have determined that there is an opposite relationship between the use of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitors and the progression of the disease (Sabbagh, 2009). Some ChE inhibitors such as donepezil, huperzine A, tacrine, and galantamine have been reported to be successful in delaying disease progression (Coutrtney et al., 2004; Davis et al., 1992; Thomsen and Kewitz, 1990; Xu et al., 1995). Researchers have so far proven that many plant species from many plant families harbor phytochemicals with ChE inhibitory activity (Ahmed et al., 2013; Ata et al., 2010).

Type 2 diabetes is a non-inherited disease characterized by high blood sugar. It usually occurs due to an unbalanced diet and a sedentary lifestyle. An increase in insulin resistance is observed in these patients (Zhang et al., 2014). One of the most effective ways to eliminate post-prandial hyperglycemia is to reduce carbohydrate absorption by inhibiting α-amylase and α-glucosidase responsible for carbohydrate digestion in type 2 diabetes patients (Bhandari et al., 2008; Shim et al., 2003). Acarbose is one of the most effective α-amylase/α-glucosidase inhibitors known today. However, since it exhibits undesirable side effects on many organs, especially the liver, the use of this molecule in the treatment of type 2 diabetes is unlikely (Tundis et al., 2010). At the same time, oxidative stress is one of the main factors that complicate the treatment of type 2 diabetes

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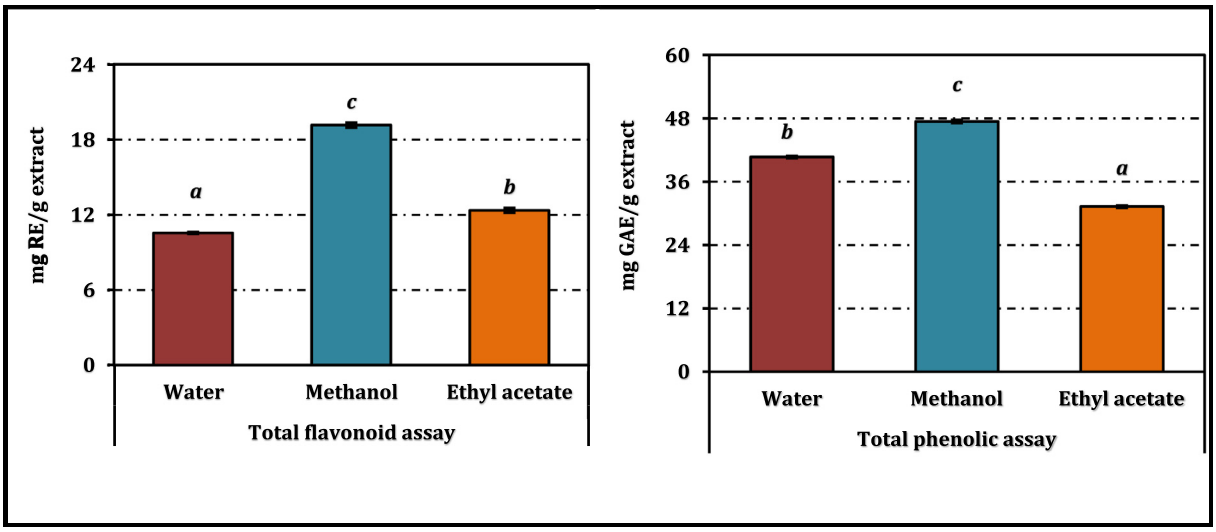

Figure 1. Total flavonoid and phenolic contents of *A. spinosus* extracts. RE and GAE: Rutin and gallic acid equivalents, respectively. Values indicated by the same superscripts are not different from the honestly significant difference after Tukey's hoc test at a 5% significance level.

(Hemalatha et al., 2016). Therefore, researchers expect candidate molecules to exhibit antioxidant activity in addition to α-amylase/α-glucosidase inhibitory activity. For this purpose, they have started to take an intense interest in plant-derived polyphenols in recent years (Pradeep and Sreerama, 2018).

Melanin, a heteropolymer of indole compounds, is synthesized in melanosomes via tyrosinase (precursor). Studies have revealed that some enzymes (e.g., TRP-1 and TRP-2) contribute to the production of this pigment (Hearing and Jiménez, 1987; Jimenez et al., 1991; Tsukamoto et al., 1992). Excessive melanin synthesis leads to the formation of unwanted spots on the skin and the browning of freshly cut vegetables and fruits. Therefore, suppressing the melanogenesis biosynthetic pathway (e.g., via tyrosinase inhibitors) is critical for both the cosmetic and food industries (Masamoto et al., 2003).

This study aimed to determine the chemical composition of extracts from the aerial parts of *Acanthus spinosus* (L.) and to document theirs *in vitro* antioxidant and enzyme inhibitory activities.

2. Materials and methods

2.1. Plant material and extract preparation

A. spinosus was collected from Kavaklidere, Çayboyu Neighborhood, Mugla-Turkey (760 m, K 37°29 797' D 028°19 112'). Dr. Olcay Ceylan (Mugla Sitki Kocman University) performed the identification of the species (Herbarium no: O.1620).

Aerial parts of the plants were used as the study material to obtain solvent extracts. Yields of the EtOAc, MeOH and water extracts were determined as 10.79, 8.77, and 9.75% (w/w), respectively. Details of the extraction procedure can be found in the supplementary file.

2.2. Determination of the phenolic compositions of the extracts

Details of the spectrophotometric and chromatographic methods were given in the supplementary file (Mollica et al., 2018).

2.3. Biological activity

The antioxidant and enzyme inhibitory activities of the extracts were determined using the methods specified in the literature (Apak et al., 2006; Kocak et al., 2016; Ozer et al., 2018; Tepe et al., 2011; Zengin et al., 2015). Details of the methods used were included in the supplementary file.

2.4. Statistical analysis

Details of the statistical analysis were presented in the supplementary file.

Table 1
Concentration (μg/g extract) of selected phenolic compounds in *A. spinosus* extracts.

Compound	Extracts		
	EtOAc	MeOH	Water
Gallic acid	4.1±0.3	33.9±0.5^{a}	17.2±0.6^{b}
Protocatechuic acid	93.8±1.0^{c}	889±1^{a}	333±2^{b}
3.4-Dihydroxyphenylacetic acid	13.3±0.2^{b}	35.1±3.3^{a}	17.2±0.2^{b}
Pyrocatechol	39.3±0.7^{c}	174±5^{b}	227±3^{a}
(+)-Catechin	nd	8.4±0.1	nd
Chlorogenic acid	6.2±0.2^{b}	9.2±0.2^{a}	4.2±0.1^{c}
2.5-Dihydroxybenzoic acid	13.8±0.2^{c}	28.2±1.2^{b}	48.7±0.2^{a}
4-Hydroxybenzoic acid	167±2^{c}	979±13^{a}	286±4^{b}
(-)-Epicatechin	2.4±0.1^{a}	2.4±0.1^{a}	2.4±0.1^{a}
Vanillic acid	449±31^{b}	4342±37^{a}	309±11^{c}
Caffeic acid	17.9±0.3^{c}	272±2^{a}	114±5^{b}
Syringic acid	119±15^{c}	1272±19^{a}	478±1^{b}
3-Hydroxybenzoic acid	14.1±0.4^{a}	15.7±1.6^{a}	8.2±0.3^{b}
Vanillin	94±1^{b}	133±4^{a}	11.1±0.3^{c}
Verbascoside	287±20^{b}	28979±267^{a}	120±1^{b}
Taxifolin	9.7±0.1^{b}	14.6±0.2^{a}	7.4±0.2^{c}
p-Coumaric acid	54.8±3.3^{c}	653±3^{a}	125±2^{b}
Sinapic acid	7.3±0.5^{c}	98±10^{b}	144±1^{a}
Ferulic acid	27.2±0.3^{c}	467±3^{a}	218±8^{b}
Luteolin 7-glucoside	3.3±0.2^{b}	44.5±0.4^{a}	nd
Hesperidin	10.2±0.2^{b}	732±1^{a}	0.88±0.05^{c}
Rosmarinic acid	11.5±0.1^{b}	14.2±0.5^{a}	7.8±0.1^{c}
Hyperoside	8.8±0.2^{b}	267±1^{a}	1.6±0.1^{c}
Apigenin 7-glucoside	4.4±0.1^{b}	29.9±1.1^{a}	nd
2-Hydroxycinnamic acid	4.0±0.01^{a}	2.4±0.1^{c}	3.3±0.2^{b}
Pinoresinol	nd	3211±17^{a}	495±21^{b}
Eriodictyol	17.6±0.1^{c}	73±2^{a}	27.9±0.7^{b}
Quercetin	4.4±0.1^{c}	29.5±0.1^{a}	8.3±0.1^{b}
Luteolin	101±1^{b}	407±1^{a}	54.1±0.9^{c}
Kaempferol	262±1^{b}	1170±19^{a}	67.1±0.2^{c}
Apigenin	76±1^{b}	153±2^{a}	7.2±0.1^{c}

The values indicated by the same superscripts within the same row are not different according to Tukey's honestly significant difference post hoc test at a 5% significance level. nd: Not detected.

3. Results and discussion

3.1. Chemical compositions of the extracts

The chemical composition of *A. spinosus* species was analyzed qualitatively and quantitatively by using spectrophotometric and chromatographic methods. The total amounts of phenolics and flavonoids were given in Figure 1, respectively.

According to the data in Figure 1, the MeOH extract was found to be richer in terms of both compound groups than the other extracts. The total phenolic and flavonoid contents of the MeOH extract were 47.4 mg GAE/g and 19.6 mg RE/g, respectively. On the other hand, while the lowest extract in terms of phenolics was obtained with EtOAc (31.3 mg GAE/g), the lowest extract in flavonoids was determined as water extract (10.6 mg RE/g).

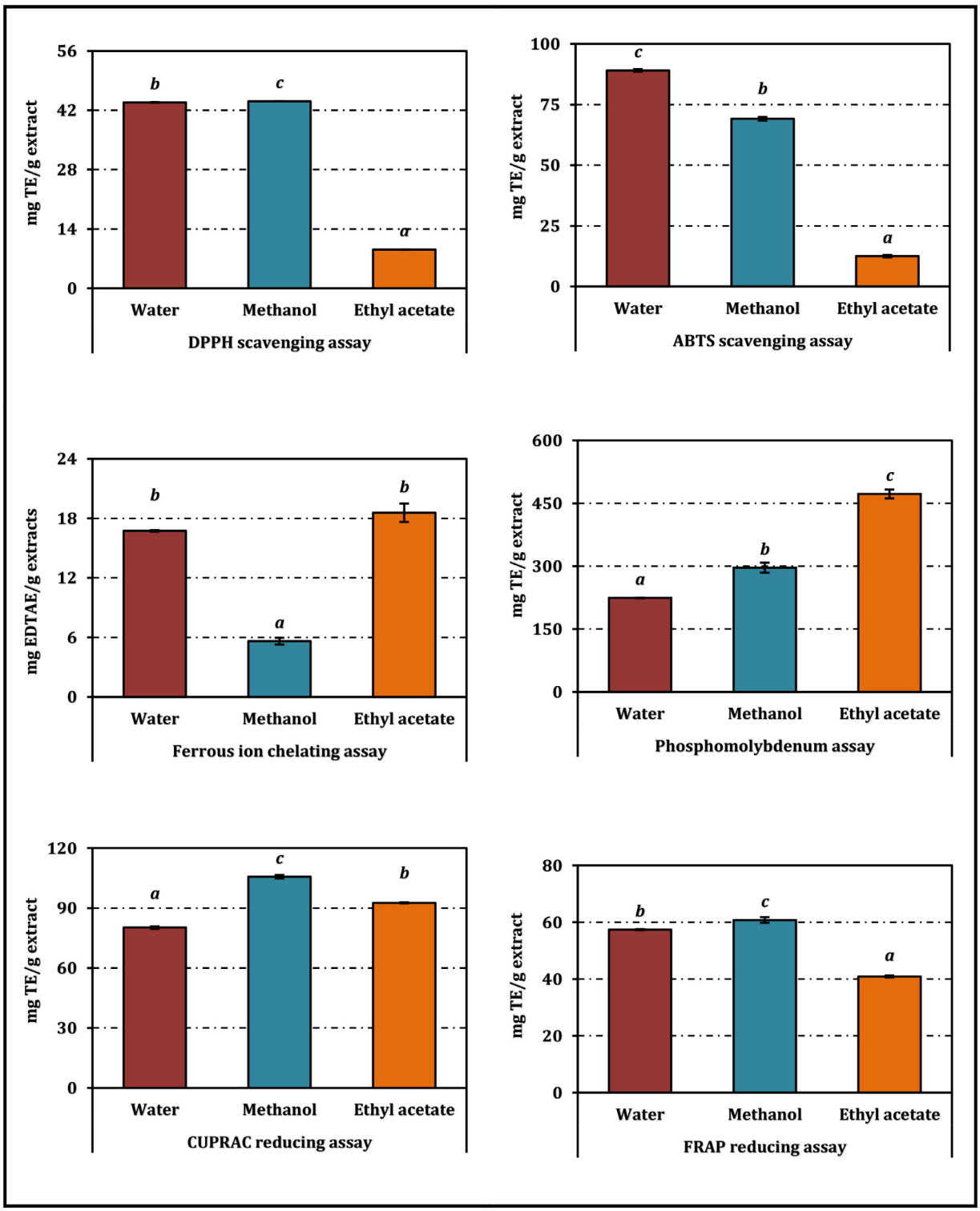

Figure 2. Antioxidant activity of *A. spinosus* extracts [TE and EDTAE mean Trolox and ethylenediaminetetraacetic acid (disodium salt) equivalents, respectively]. Values indicated by the same superscripts are not different from the honestly significant difference after Tukey's hoc test at a 5% significance level.

The phytochemical composition data of the extracts obtained as a result of chromatographic analyzes were given in Table 1.

The data in Table 1 generally overlapped with the quantitative data given in Figure 1. Chromatographic analyzes confirmed that the MeOH extract was richer in most of the phytochemicals in the table than the other extracts. According to the table, verbascoside (28979 μg/g), vanillic acid (4342 μg/g), pinoresinol (3211 μg/g), syringic acid (1272 μg/g), and kaempferol (1170 μg/g) were the most abundant phytochemicals in the MeOH extract. In addition, the extract also contained significant amounts of protocatechuic and 4-hydroxybenzoic acids.

According to the results of the literature research, there is no data on the chemical composition of the plant species analyzed in the current study. Therefore, the phytochemical composition of *A. spinosus* was brought to the literature for the first time with this study.

3.2. Antioxidant activities of the extracts

The antioxidant activities of the extracts were analyzed by performing radical scavenging, phosphomolybdenum, reducing power, and chelating effect tests, respectively (Figure 2). Since the data obtained from each test are expressed in different units, the relative antioxidant activity capacity (RACI) test was applied to evaluate all these data together and rank the extracts in terms of their activities (Figure 3). In addition to the RACI values obtained, the correlation between each RACI coefficient and the antioxidant activities of the extracts was also presented in Figure 4.

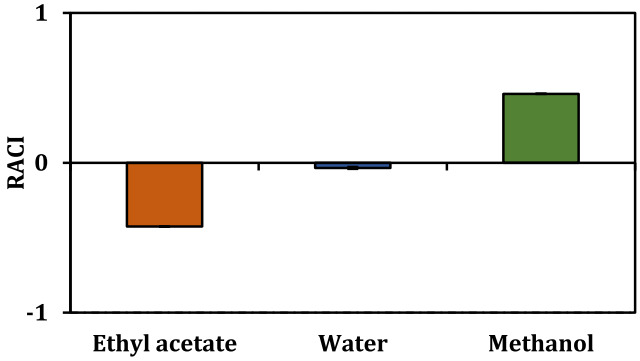

Figure 3. Relative antioxidant capacity index of *A. spinosus* extracts.

In radical scavenging assay, the scavenging capacity of the extracts on ABTS was higher than on DPPH. In DPPH radical scavenging test, the activity values of water and MeOH extracts were almost equal to each other (43.9 and 44.1 mg TEs/g, respectively), while the ABTS radical scavenging test resulted in the superiority of the water extract (89.1 mg TE/g).

EtOAc extract took first place in the phosphomolybdenum test, in which total antioxidant activity was analyzed (4730 TE/g). It was

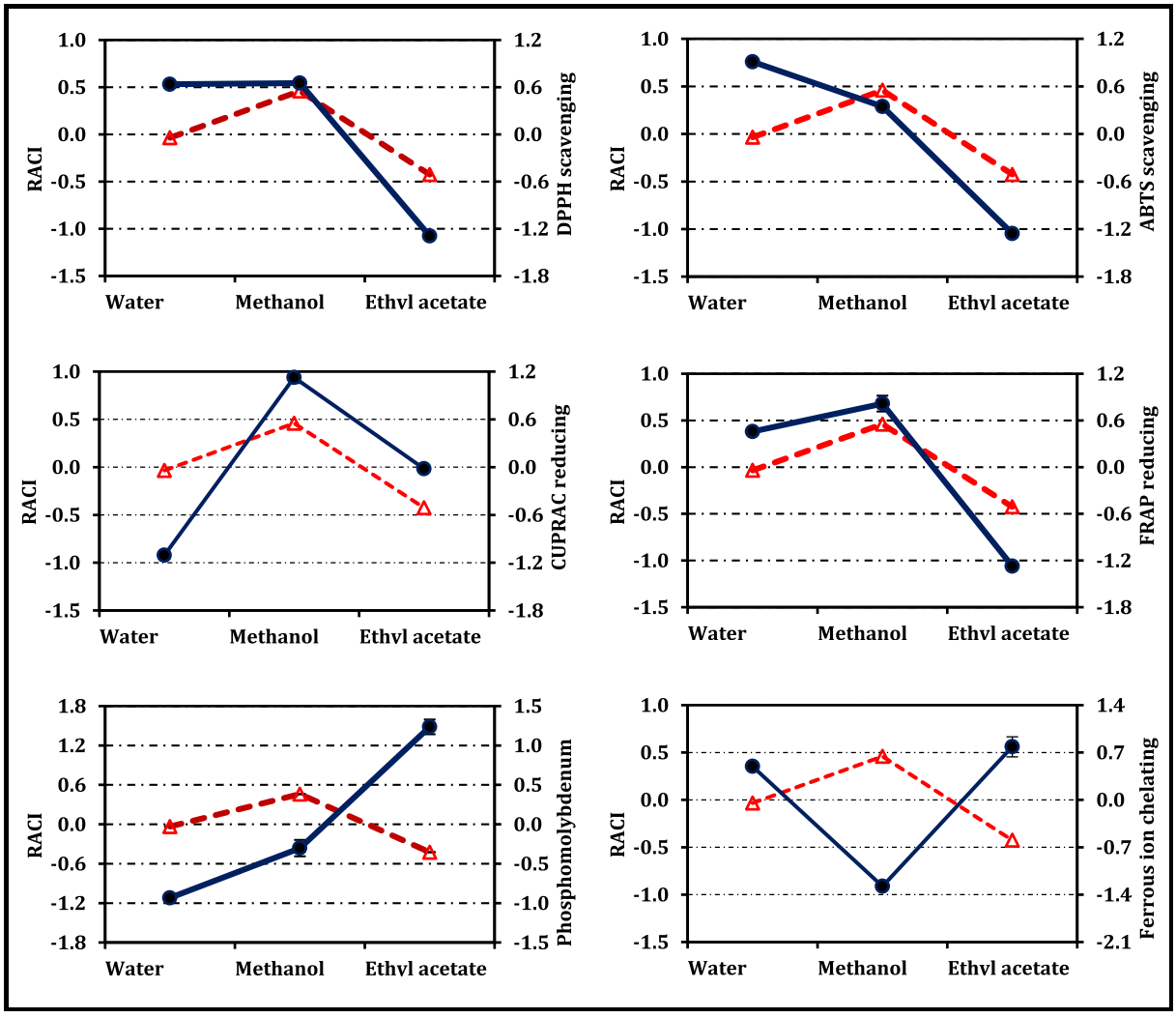

Figure 4. Relative antioxidant capacity index (dashed red line with the triangle) and antioxidant activity (solid dark blue line with circle) of *A. spinosus* extracts.

followed by the MeOH extract with 296 mg TE/g. A similar activity profile was detected in the ferrous ion chelating activity test. In this test, as in the phosphomolybdenum assay, the EtOAc extract exhibited the highest activity (18.6 mg of EDTAE/g). The chelating capacity of the water extract was found to be very close to that of the EtOAc extract (16.7 mg EDTAE/g). In many previous studies by our research group, it has been determined that the activity profile obtained from the ferrous ion chelating assay and those obtained from other antioxidant activity tests are quite different from each other (Carev and Sarikurkcu, 2021; Zengin et al., 2021). Based on these data, the molecules responsible for the chelating activity are thought to probably have low polarity.

In the CUPRAC and FRAP tests, where the reducing powers of the extracts were analyzed, the MeOH extract exhibited the strongest activity. The activities of the MeOH extract in the CUPRAC and FRAP test systems were 106 and 61 mg TE/g, respectively. Water and EtOAc extracts showed the weakest activity in these tests (80 and 40.9 mg TE/g, respectively).

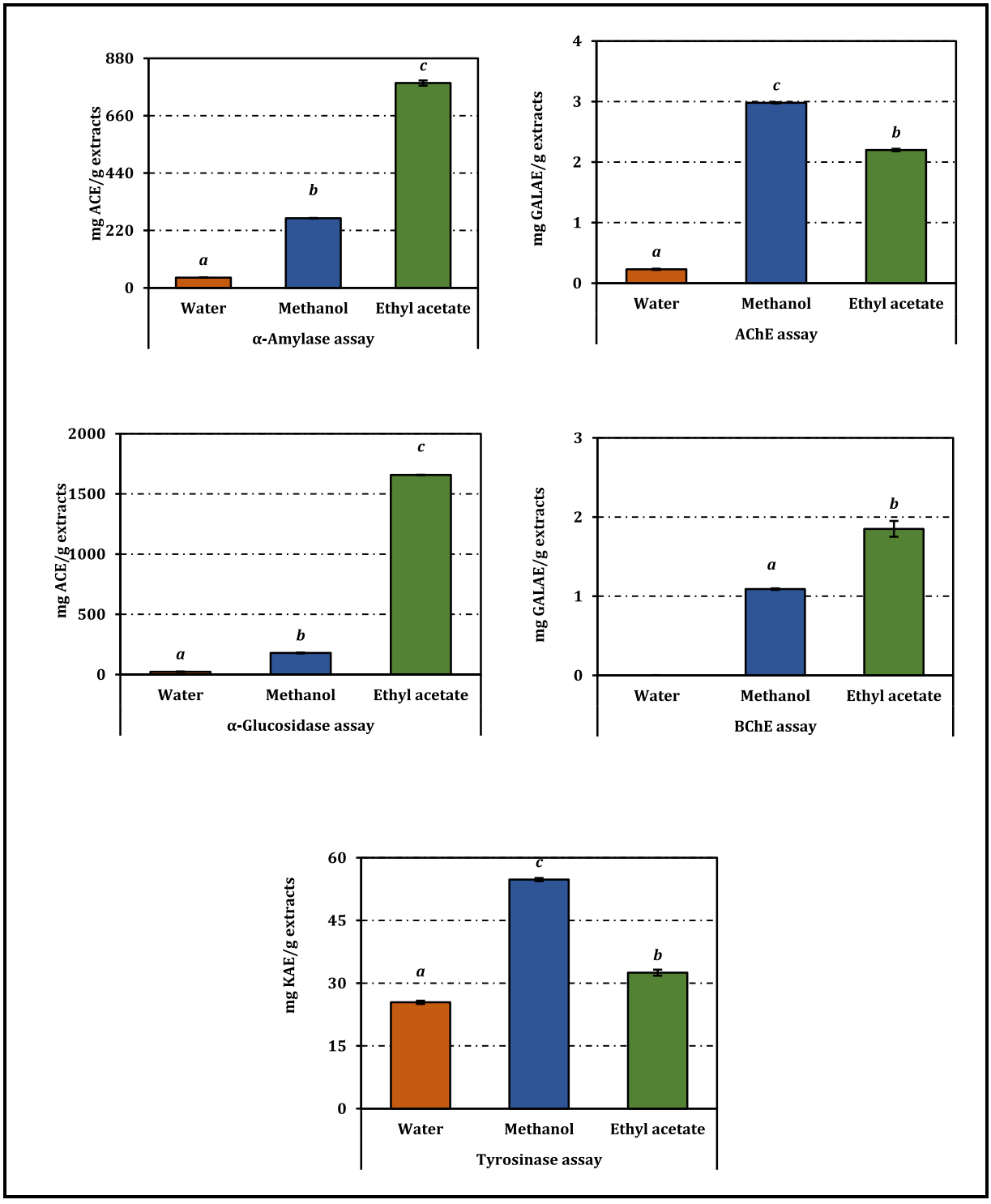

Figure 5. Enzyme inhibition activity of *A. spinosus* extracts. ACE, GALAE, and KAE mean acarbose, galanthamine, and kojic acid equivalents, respectively. Values indicated by the same superscripts are not different from the honestly significant difference after Tukey's hoc test at a 5% significance level.

Since an activity-based chromatographic system was not applied in the current study, it would be more appropriate to make a literature review regarding the contribution of the major compounds given in Table 1 to the activity. Literature data show that verbascoside (D'Imperio et al., 2014; Funes et al., 2009; Vertuani et al., 2011), vanillic acid (Emmons et al., 1999; McDonald et al., 2001; Zheng and Wang, 2001), pinoresinol (López-Biedma et al., 2016; Wan et al., 2015; Youssef et al., 2020), syringic acid (Belkheiri et al., 2010; Cikman et al., 2015; Papadopoulos and Boskou, 1991) and kaempferol (Deng et al., 2019; Jung et al., 2009), which are among the major components in the extracts, can contribute significantly to the antioxidant activity.

3.3. Enzyme inhibitory activities of the extracts

The inhibitory activity potentials of the extracts on CHEs, α-amylase/α-glucosidase, and tyrosinase were given in Figure 5.

The inhibitory activities of the extracts on AChE were found to be stronger than on BChE. The highest inhibitory activity on AChE was exhibited by the MeOH extract (3.0 mg GALAE/g). It was followed by the EtOAc and water extracts followed (2.2 and 0.2 mg GALAE/g, respectively). The BChE inhibitory activity test resulted in the superiority of the EtOAc extract (1.8 mg GALAE/g). The water extract did not show any activity in this test system.

In the α-amylase/α-glucosidase inhibitory activity tests, in which the antidiabetic activities of the extracts were investigated, higher inhibitory activity against α-glucosidase was obtained. In both test systems, the EtOAc extract exhibited the highest activity (785 and 1658 ACE/g, respectively). The water extract showed the weakest activity against both enzymes (39.2 and 23.2 mg ACE/g, respectively).

The tyrosinase inhibitory activity test, in which the skin whitening activities of the extracts were tested, resulted in the superiority of MeOH extract (54.8 mg KAE/g). It was followed by EtOAc (32.5 mg KAE/g) and water extracts (25.4 mg KAE/g), respectively.

According to the data in Table 1, verbascoside is present in high amounts in both MeOH and EtOAc extracts. There are some reports in the literature that this compound may show ChE inhibitory activity or may contribute to the ChE inhibitory activities of the extracts it contains (Alipieva et al., 2014; Burgos et al., 2020; Georgiev et al., 2011). In addition, there are some reports that the high content of vanillic acid (Işık and Beydemir, 2020; Szwajgier and Borowiec, 2012) and kaempferol (Bahrani et al., 2014; Beg et al., 2018) in the EtOAc extract may also contribute to ChE-inhibitory activity.

With a similar approach, it is possible to discuss literature data on phytochemicals that contribute to the α-amylase/α-glucosidase inhibitory activity of EtOAc extract. Collado-González et al. (2017) reported that verbascoside exhibited strong inhibitory activity on both enzymes. Several other reports are supporting this finding (Angeloni et al., 2021; Tlili and Sarikurkcu, 2020).

Finally, compounds that may contribute to tyrosinase inhibitory activity were discussed in this section. Just as in the AChE inhibitory activity test, the MeOH extract showed strong activity in the tyrosinase inhibitory activity test. It is thought that this activity may be due to the high amount of verbascoside in the extract. Literature data are supporting this finding. According to Son et al. (2011), verbascoside inhibited monophenolase activity in a dose-dependent manner. However, more detailed analyzes are needed to detect other compounds that contribute to the activity.

4. Conclusions

In this study, the chemical composition and *in vitro* antioxidant and enzyme inhibitory activities of EtOAc, MeOH, and water extracts obtained from the aerial parts of *A. spinosus* were investigated. It is thought that MeOH extract exhibits an antioxidant, AChE, and tyrosinase inhibitory activity profile proportional to its rich phytochemical content. Additionally, it was concluded that EtOAc extract could be an effective inhibitor of ChE, α-amylase, and α-glucosidase.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.sajb.2021.11.006.

References

Ahmed, F., Ghalib, R.M., Sasikala, P., Ahmed, K.M., 2013. Cholinesterase inhibitors from botanicals. Pharmacognosy Reviews 7, 121.

Alipieva, K., Korkina, L., Orhan, I.E., Georgiev, M.I., 2014. Verbascoside—A review of its occurrence,(bio) synthesis and pharmacological significance. Biotechnology Advances 32, 1065–1076.

Angeloni, S., Spinozzi, E., Maggi, F., Sagratini, G., Caprioli, G., Borsetta, G., Ak, G., Sinan, K.I., Zengin, G., Arpini, S., 2021. Phytochemical Profile and Biological Activities of Crude and Purified Leonurus cardiaca Extracts. Plants 10, 195.

Apak, R., Güçlü, K., Özyürek, M., Esin Karademir, S., Erçağ, E., 2006. The cupric ion reducing antioxidant capacity and polyphenolic content of some herbal teas. Int. J. Food Sci. Nutr. 57, 292–304.

Ata, A., Iverson, C.D., Kalhari, K.S., Akhter, S., Betteridge, J., Meshkatalsadat, M.H., Orhan, I., Sener, B., 2010. Triterpenoidal alkaloids from *Buxus hyrcana* and their enzyme inhibitory, anti-fungal and anti-leishmanial activities. Phytochemistry 71, 1780–1786.

Bahrani, H., Mohamad, J., Paydar, M.J., Rothan, H.A., 2014. Isolation and characterisation of acetylcholinesterase inhibitors from *Aquilaria subintegra* for the treatment of Alzheimer's disease (AD). Current Alzheimer Research 11, 206–214.

Beg, T., Jyoti, S., Naz, F., Ali, F., Ali, S.K., Reyad, A.M., Siddique, Y.H., 2018. Protective effect of kaempferol on the transgenic *Drosophila* model of Alzheimer's disease. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders) 17, 421–429.

Belkheiri, N., Bouguerne, B., Bedos-Belval, F., Duran, H., Bernis, C., Salvayre, R., Nègre-Salvayre, A., Baltas, M., 2010. Synthesis and antioxidant activity evaluation of a syringic hydrazones family. European Journal of Medicinal Chemistry 45, 3019–3026.

Bhandari, M.R., Jong-Anurakkun, N., Hong, G., Kawabata, J., 2008. α-Glucosidase and α-amylase inhibitory activities of Nepalese medicinal herb Pakhanbhed (*Bergenia ciliata*. Haw.). Food Chemistry 106, 247–252.

Boo, Y.C., 2019. Can plant phenolic compounds protect the skin from airborne particulate matter? Antioxidants 8, 379.

Burgos, C., Muñoz-Mingarro, D., Navarro, I., Martín-Cordero, C., Acero, N., 2020. Neuroprotective Potential of Verbascoside Isolated from *Acanthus mollis* L. Leaves through Its Enzymatic Inhibition and Free Radical Scavenging Ability. Antioxidants 9, 1207.

Carev, I., Sarikurkcu, C., 2021. LC-MS/MS Profiles and *In Vitro* Biological Activities of Extracts of an Endemic Species from Turkey: Stachys *cretica* ssp. *anatolica*. Plants 10, 1054.

Cikman, O., Soylemez, O., Ozkan, O.F., Kiraz, H.A., Sayar, I., Ademoglu, S., Taysi, S., Karaayvaz, M., 2015. Antioxidant activity of syringic acid prevents oxidative stress in l-arginine–induced acute pancreatitis: An experimental study on rats. International surgery 100, 891–896.

Collado-González, J., Grosso, C., Valentão, P., Andrade, P.B., Ferreres, F., Durand, T., Guy, A., Galano, J.-M., Torrecillas, A., Gil-Izquierdo, Á., 2017. Inhibition of α-glucosidase and α-amylase by Spanish extra virgin olive oils: The involvement of bioactive compounds other than oleuropein and hydroxytyrosol. Food Chemistry 235, 298–307.

Coutrtney, C., Farrell, D., Gray, R., 2004. AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomized double-blind trials. Lancet 363, 2105–2115.

D'Imperio, M., Cardinali, A., D'Antuono, I., Linsalata, V., Minervini, F., Redan, B., Ferruzzi, M., 2014. Stability–activity of verbascoside, a known antioxidant compound, at different pH conditions. Food Research International 66, 373–378.

Davis, K.L., Thal, L.J., Gamzu, E.R., Davis, C.S., Woolson, R.F., Gracon, S.I., Drachman, D.A., Schneider, L.S., Whitehouse, P.J., Hoover, T.M., 1992. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. New England Journal of Medicine 327, 1253–1259.

Deng, S.-P., Yang, Y.-L., Cheng, X.-X., Li, W.-R., Cai, J.-Y., 2019. Synthesis, spectroscopic study and radical scavenging activity of kaempferol derivatives: Enhanced water solubility and antioxidant activity. International Journal of Molecular Sciences 20, 975.

Emmons, C.L., Peterson, D.M., Paul, G.L., 1999. Antioxidant capacity of oat (*Avena sativa* L.) extracts. 2. *In vitro* antioxidant activity and contents of phenolic and tocol antioxidants. Journal of Agricultural and Food Chemistry 47, 4894–4898.

Funes, L., Fernández-Arroyo, S., Laporta, O., Pons, A., Roche, E., Segura-Carretero, A., Fernández-Gutiérrez, A., Micol, V., 2009. Correlation between plasma antioxidant capacity and verbascoside levels in rats after oral administration of lemon verbena extract. Food Chemistry 117, 589–598.
Georgiev, M., Alipieva, K., Orhan, I., Abrashev, R., Denev, P., Angelova, M., 2011. Antioxidant and cholinesterases inhibitory activities of *Verbascum xanthophoeniceum* Griseb. and its phenylethanoid glycosides. Food Chemistry 128, 100–105.
Hearing, V.J., Jiménez, M., 1987. Mammalian tyrosinase—the critical regulatory control point in melanocyte pigmentation. International Journal of Biochemistry 19, 1141–1147.
Hemalatha, P., Bomzan, D.P., Rao, B.S., Sreerama, Y.N., 2016. Distribution of phenolic antioxidants in whole and milled fractions of quinoa and their inhibitory effects on α-amylase and α-glucosidase activities. Food Chemistry 199, 330–338.
Işık, M., Beydemir, Ş., 2020. The impact of some phenolic compounds on serum acetylcholinesterase: kinetic analysis of an enzyme/inhibitor interaction and molecular docking study. Journal of Biomolecular Structure and Dynamics 1–9.
Jimenez, M., Tsukamoto, K., Hearing, V., 1991. Tyrosinases from two different loci are expressed by normal and by transformed melanocytes. Journal of Biological Chemistry 266, 1147–1156.
Jung, H.A., Woo, J.J., Jung, M.J., Hwang, G.-S., Choi, J.S., 2009. Kaempferol glycosides with antioxidant activity from *Brassica juncea*. Archives of Pharmacal Research 32, 1379–1384.
Kocak, M.S., Sarikurkcu, C., Cengiz, M., Kocak, S., Uren, M.C., Tepe, B., 2016. *Salvia cadmica*: Phenolic composition and biological activity. Ind. Crops Prod. 85, 204–212.
López-Biedma, A., Sánchez-Quesada, C., Beltrán, G., Delgado-Rodríguez, M., Gaforio, J.J., 2016. Phytoestrogen (+)-pinoresinol exerts antitumor activity in breast cancer cells with different oestrogen receptor statuses. BMC Complementary and Alternative Medicine 16, 1–14.
Masamoto, Y., Ando, H., Murata, Y., Shimoishi, Y., Tada, M., Takahata, K., 2003. Mushroom tyrosinase inhibitory activity of esculetin isolated from seeds of *Euphorbia lathyris* L. Bioscience Biotechnology, and Biochemistry 67, 631–634.
McDonald, S., Prenzler, P.D., Antolovich, M., Robards, K., 2001. Phenolic content and antioxidant activity of olive extracts. Food Chemistry 73, 73–84.
Melnikova, I., 2007. Therapies for Alzheimer's disease. Nature Reviews Drug Discovery 6, 341–342.
Mollica, A., Zengin, G., Stefanucci, A., Ferrante, C., Menghini, L., Orlando, G., Brunetti, L., Locatelli, M., Dimmito, M.P., Novellino, E., 2018. Nutraceutical potential of Corylus avellana daily supplements for obesity and related dysmetabolism. Journal of Functional Foods 47, 562–574.
Ozer, M.S., Kirkan, B., Sarikurkcu, C., Cengiz, M., Ceylan, O., Atilgan, N., Tepe, B., 2018. *Onosma heterophyllum*: Phenolic composition, enzyme inhibitory and antioxidant activities. Industrial Crops and Products 111, 179–184.
Papadopoulos, G., Boskou, D., 1991. Antioxidant effect of natural phenols on olive oil. Journal of the American Oil Chemists' Society 68, 669–671.
Pawlowska, E., Szczepanska, J., Koskela, A., Kaarniranta, K., Blasiak, J., 2019. Dietary polyphenols in age-related macular degeneration: protection against oxidative stress and beyond. Oxidative Medicine and Cellular Longevity, 9682318 2019.
Pradeep, P., Sreerama, Y.N., 2018. Phenolic antioxidants of foxtail and little millet cultivars and their inhibitory effects on α-amylase and α-glucosidase activities. Food Chemistry 247, 46–55.
Sabbagh, M.N., 2009. Drug development for Alzheimer's disease: where are we now and where are we headed? The American Journal of Geriatric Pharmacotherapy 7, 167–185.
Shim, Y.-J., Doo, H.-K., Ahn, S.-Y., Kim, Y.-S., Seong, J.-K., Park, I.-S., Min, B.-H., 2003. Inhibitory effect of aqueous extract from the gall of *Rhus chinensis* on alpha-glucosidase activity and postprandial blood glucose. Journal of Ethnopharmacology 85, 283–287.
Son, Y.-O., Lee, S.-A., Kim, S.-S., Jang, Y.-S., Chun, J.-C., Lee, J.-C., 2011. Acteoside inhibits melanogenesis in B16F10 cells through ERK activation and tyrosinase down-regulation. Journal of Pharmacy and Pharmacology 63, 1309–1319.
Szwajgier, D., Borowiec, K., 2012. Phenolic acids from malt are efficient acetylcholinesterase and butyrylcholinesterase inhibitors. Journal of the Institute of Brewing 118, 40–48.
Tepe, B., Sarikurkcu, C., Berk, S., Alim, A., Akpulat, H.A., 2011. Chemical composition, radical scavenging and antimicrobial activity of the essential oils of *Thymus boveii* and *Thymus hyemalis*. Records of Natural Products 5, 208–220.
Thomsen, T., Kewitz, H., 1990. Selective inhibition of human acetylcholinesterase by galanthamine *in vitro* and *in vivo*. Life Sciences 46, 1553–1558.
Tlili, N., Sarikurkcu, C., 2020. Bioactive compounds profile, enzyme inhibitory and antioxidant activities of water extracts from five selected medicinal plants. Industrial Crops and Products 151, 112448.
Tsukamoto, K., Jackson, I.J., Urabe, K., Montague, P.M., Hearing, V.J., 1992. A second tyrosinase-related protein, TRP-2, is a melanogenic enzyme termed DOPAchrome tautomerase. The EMBO Journal 11, 519–526.
Tundis, R., Loizzo, M., Menichini, F., 2010. Natural products as α-amylase and α-glucosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: an update. Mini Reviews in Medicinal Chemistry 10, 315–331.
Vertuani, S., Beghelli, E., Scalambra, E., Malisardi, G., Copetti, S., Toso, R.D., Baldisserotto, A., Manfredini, S., 2011. Activity and stability studies of verbascoside, a novel antioxidant, in dermo-cosmetic and pharmaceutical topical formulations. Molecules 16, 7068–7080.
Wan, Y., Li, H., Fu, G., Chen, X., Chen, F., Xie, M., 2015. The relationship of antioxidant components and antioxidant activity of sesame seed oil. Journal of the Science of Food and Agriculture 95, 2571–2578.
Xu, S.-S., Gao, Z.-X., Weng, Z., Du, Z.-M., Xu, W.-A., Yang, J.-S., Zhang, M.-L., Tong, Z.-H., Fang, Y.-S., Chai, X.-S., 1995. Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Acta Pharmacologica Sinica 16, 391–395.
Youssef, F.S., Ashour, M.L., El-Beshbishy, H.A., Ahmed Hamza, A., Singab, A.N.B., Wink, M., 2020. Pinoresinol-4-O-β-D-glucopyranoside: a lignan from prunes (Prunus domestica) attenuates oxidative stress, hyperglycaemia and hepatic toxicity *in vitro* and *in vivo*. Journal of Pharmacy and Pharmacology 72, 1830–1839.
Zengin, G., Mahomoodally, M.F., Aktumsek, A., Jekő, J., Cziáky, Z., Rodrigues, M.J., Custodio, L., Polat, R., Cakilcioglu, U., Ayna, A., 2021. Chemical Profiling and Biological Evaluation of *Nepeta baytopii* Extracts and Essential Oil: An Endemic Plant from Turkey. Plants 10, 1176.
Zengin, G., Sarikurkcu, C., Gunes, E., Uysal, A., Ceylan, R., Uysal, S., Gungor, H., Aktumsek, A., 2015. Two *Ganoderma* species: Profiling of phenolic compounds by HPLC-DAD, antioxidant, antimicrobial and inhibitory activities on key enzymes linked to diabetes mellitus, Alzheimer's disease and skin disorders. Food Funct 6, 2794–2802.
Zhang, J., Zhao, S., Yin, P., Yan, L., Han, J., Shi, L., Zhou, X., Liu, Y., Ma, C., 2014. α-Glucosidase inhibitory activity of polyphenols from the burs of *Castanea mollissima* Blume. Molecules 19, 8373–8386.
Zheng, W., Wang, S.Y., 2001. Antioxidant activity and phenolic compounds in selected herbs. Journal of Agricultural and Food chemistry 49, 5165–5170.
Zhou, Y., Jiang, Z., Lu, H., Xu, Z., Tong, R., Shi, J., Jia, G., 2019. Recent advances of natural polyphenols activators for Keap1-Nrf2 signaling pathway. Chemistry & Biodiversity 16, e1900400.