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ORIGINAL RESEARCH

Antioxidant activities of *Alyssum virgatum* plant and its main components

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Abstract

The antioxidant properties of methanol extract of above-ground parts of *Alyssum virgatum*, an endemic plant, were analyzed. Together with their total phenolic, flavonoid, and antioxidant capacities, their effects on reactive oxygen species were determined by experimental methods. The methanol extracts of *A. virgatum* plant appeared to exhibit in-vitro antioxidant activity. In particular, the extract of the plant was found to have a scavenging effect against hydrogen peroxide and hydroxyl radical. Total phenolic content was found to be 161.25 mg gallic acid per gram dry material. Total flavonoid content was found to be 119.89 mg quercetin per gram dry material. Total antioxidant capacity was determined as 94.92 mM α-tocopherol acetate per gram dry material. Moreover, the amount of the extract that caused 50% inhibition of hydrogen peroxide and hydroxyl radical was assayed as 29.24 mg mL^{-1} and 46.04 mg mL^{-1}, respectively.

Addition to the experimental studies, DFT, molecular docking, and ADME calculations were performed to determine antioxidant, biological activity, and drug properties of two main phenolic components of *A. virgatum* which are cinnamic acid and ferulic acid. DFT calculations were executed at B3LYP/6–311 + + G(d,p) level in Gaussian 16 software. The HAT, SET-PT, SPLET mechanisms, and the spin density analyses of the main components were investigated in detail. Molecular docking studies of the investigated main components were executed on the antioxidant proteins in Schrodinger 2020–3 program. Additionally, ADME properties of the mentioned main components were determined via QikProp module in the Schrodinger software. All theoretical studies showed that ferulic acid had better antioxidant, biological, and drug activities than cinnamic acid.

Keywords *Alyssum virgatum* · Methanolic extract · Antioxidant · DFT · Molecular docking · ADME

Introduction

Brassicaceae family contains plenty of genders, *Crambe* [1], *Sinapis* [2], *Thlaspi* [3], *Alyssum* [4], and *Brassica* [5]. Regarding its antioxidant, antibacterial, and anticancer properties, family members are rich in terms of various biologically active molecules, such as glucosinolates, flavonoids, phenolic acids, and vitamins [6]. Glucosinolates are secondary metabolites containing sulfur and nitrogen and they have properties to inhibit tumorigenesis in various types of cancer. Phenolic compounds with antioxidant and antimicrobial properties are also quite common in this family [7].

With the number of its species up to 230, the *Alyssum* L. genus is among the largest known genera in the world and its main distribution area is Eastern Europe and Turkey [8]. This genus is among the large genera of Turkey's flora, and it is indicated by 90 species. Fifty-four of these species are endemic, whereas about a third of these species are endangered and in need of protection [9]. After the latest revisions, this genus was found to have approximately 110 taxa [10].

One of the important defining qualities of secondary metabolites is the fact that they are stored as complex concentrations in high concentrations, and sometimes in organs that do not produce them. Some secondary metabolites are stored as inactive "primary medicines" and they are enzymatically activated in case of risk (burning, infection). Many secondary metabolites interact with proteins, DNA/RNA,

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and/or bio membranes. Some of these interactions are very specific in terms of their molecular targets, while others have variable properties [11]. The number of primary metabolites is 2000 in humans, while it is between 5000 and 25,000 in plants. Known plant secondary metabolites are about 100,000 [12]. Based on their biosynthetic origins, plant secondary metabolites may be classed into three major groups: phenolic compounds, terpenoids, and nitrogen-containing molecules. These groups are chemically different from each other and are produced from the metabolic pathways that take place during the process of glycolysis, photosynthesis, and citric acid cycle. Secondary metabolites are synthesized via acetyl-CoA (acetyl coenzyme A), mevalonic acid, shikimic acid, and 1-deoxy-D-xylulose-5-phosphate, which are intermediate products of these processes that are the pathways of primary metabolism [13].

In HPLC analysis for *Alyssum virgatum* plant to be used in the study, cinnamic acid (2.05 ± 1.0 mg/g extract) and ferulic acid (1.85 ± 0.09 mg/g extract) are determined as two main phenolic components [14] which are given in Fig. 1.

Since the *Alyssum* L. genus distributed in Turkey is represented by quite a lot of species and the vast majority of them are endemic, the examination of the biological activities of the species of this genus and determination of its active ingredients is of great importance.

Computational chemistry is quite a popular research field in the science world [15–19]. Some properties of molecules have been estimated with the help of computational studies [20–24]. For example; density functional theory (DFT) and molecular docking studies assist to predict the antioxidant and biological activity properties of compounds, respectively [25–31]. In addition to these studies, absorption, distribution, metabolism, and excretion (ADME) results can be also used to examine the drug properties of molecules [31–35].

In this study, scavenging effects on reactive oxygen species and antioxidant activities of methanol extracts of aboveground parts of *A. virgatum*, which is an endemic plant, are analyzed by experimental methods. We experimentally compared the methanol extract of *A. virgatum* plant with curcumin which are natural antioxidant and hydroxytoluene (BHT) that are synthetic antioxidant. Besides, DFT, molecular docking, and ADME calculations are executed to interpret the antioxidant, biological, and drug activities of cinnamic acid and ferulic acid molecules which are determined as two main phenolic components of *A. virgatum*.

Methods

Experimental methods

Preparation of the extract

Air-dried *A. virgatum* plant (100 g) was shredded and extracted for approximately 4 h with methanol using a Soxhlet apparatus [36]. Then the extract was drained and evaporated to dryness in a vacuum at 45 °C. The plant extract was lyophilized and stored in the dark at + 4 °C.

Determination of total phenolic content

The total phenolic content (TPC) of the mentioned methanol extract was found by using a Folin–Ciocalteau reagent (FCR) method, according to Singleton et al. [37]. After that, the sample solution (500 µL) and 11.0 mL distilled water was mixed, undiluted FCR (250 µL) was added. After 3 min, 750 µL of 2% (w/v) sodium carbonate was mixed and then 2 h incubation at room temperature, the absorbance was measured at 760 nm. Gallic acid was preferred as a standard between 0.5 and 100 mg L^{-1}, and the results were given as milligram equivalent of the gallic acid per gram dry material.

Determination of total flavonoid content

The total flavonoid content was determined as quercetin equivalents per gram of the extract [38]. The sample solution

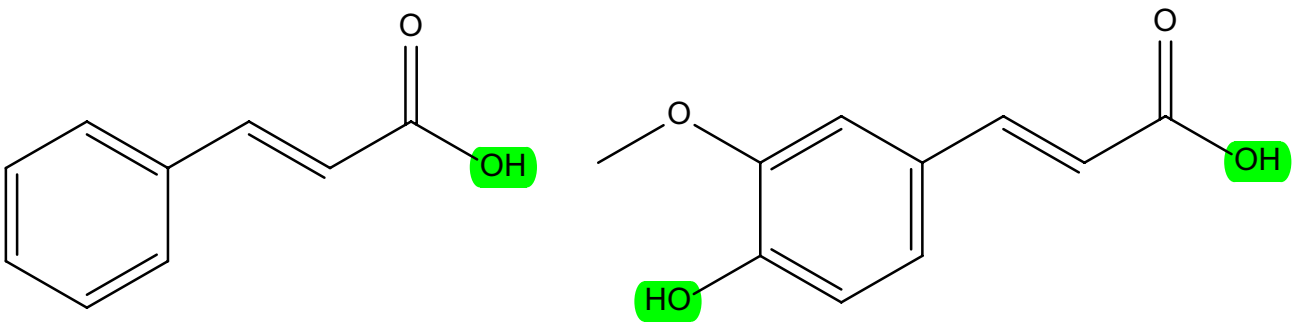

Fig. 1 The structures of two main phenolic components of *Alyssum virgatum*. Left: cinnamic acid, right: ferulic acid

in methanol (1.0 mL) was mixed with aluminum chloride %2 (1.0 mL), which was prepared in half the volume of methanol and glacial acetic acid. The mixture was incubated for 10 min at room temperature, and the absorbance was measured at 364 nm. A standard curve of quercetin ranging from 0.5 to 50 mg L^{-1} of concentrations was used to find the TFC contents of the extract. The obtained result was expressed as milligram of quercetin equivalents per gram dry material.

Determination of total antioxidant capacity

The basis of the method is based on the formation of green-colored complex of phosphate/Mo(V) in acidic pH with the reduction of acidic Mo(VI) to Mo(V) [39]. A sample solution (0.2 mL) containing reducing species methanol was combined in an Eppendorf tube with a reagent solution (2.0 mL) which include 4-mM ammonium molybdate, 28-mM sodium phosphate, and 0.6-M sulfuric acid. The tube was capped and incubated for 90 min at 95 °C. Before the absorbance of the aqueous solution of each was measured at 695 nm against a blank, the samples had cooled to room temperature. The total antioxidant capacity of the sample was standardized against α-tocopherol acetate and expressed as mM α-tocopherol acetate equivalents per gram dry material.

Scavenging activity of hydrogen peroxide

The hydrogen peroxide (H_2O_2) scavenging activity of the methanolic extracts was carried out following the procedure of Ruch et al. [40]. The solution of H_2O_2 (40 mM) was prepared in a phosphate buffer (pH 7.4). The methanolic extract of the plant was added to an H_2O_2 solution (0.6 mL, 40 mM) and incubated for 10 min at room temperature. The absorbance value of the reaction mixtures was recorded at 230 nm. A buffer solution without H_2O_2 was used as a blank. The percentage of H_2O_2 scavenging was calculated as:

$$H_2O_2 scavenging\ rate(\%) = [(A_{control} - A_{sample})/A_{control}] \times 100 \quad (1)$$

where $A_{control}$ is the absorbance of the control, and A_{sample} is the absorbance in the methanolic extracts of plants.

Scavenging activity of hydroxyl radicals

The hydroxyl radicals scavenging activity were measured by Fenton reaction [41]. The reaction mixture contained in 100 µL of 3.0-mM deoxyribose, 100 µL of 1.0-mM iron(III) chloride, 100 µL of 1.0-mM EDTA, 100 µL of 1.0-mM ascorbic acid, 100 µL of 1.0-mM hydrogen peroxide, and 500 µL of 20-mM phosphate buffer, and 2.0 mL of extract at various concentrations. The reaction mixture was incubated for 60 min at 37 °C. Afterwards, 1.0 mL of 1% thiobarbituric acid (TBA) and 1.0 mL of 2.8% trichloroacetic acid (TCA) were added to the mixture and was boiled for 30 min. The absorbance was measured as a pink malondialdehyde-TBA chromogen at 532 nm. The percentage of hydroxyl radicals scavenging activity was calculated, according to Eq. 1.

Statistical analysis

The results of the experimental part of this study were reported as the mean ± SD of three parallel measurements. The data were statistically analyzed by one-way ANOVA program. The values of $p < 0.05$ were considered statistically significant.

Theoretical methods

DFT calculations

The antioxidant properties of phenolic molecules can be explained via mechanisms which are called hydrogen atom transfer (HAT), single electron transfer followed by proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET) reactions [42–46]. In each of these mechanisms, the radical scavenging abilities of phenolic compounds can be determined. Firstly, HAT mechanism performed in the one-step reaction is given in Eq. 2.

$$R\cdot + ArOH \rightarrow RH + ArO \quad (2)$$

From Eq. 2, it is seen that the phenolic compound (ArOH) by giving a hydrogen atom to free radical ($R^{\cdot}$) via homolytic breaking of the O–H bond quench the radical. The weaker the O–H bond means the easier the radical scavenging. Therefore, the antioxidant activity of ArOH can be estimated with bond dissociation enthalpy (BDE) of the O–H bond.

The second mechanism is SET-PT reactions consisting of two steps as shown in Eq. 2. Its first step is based on the electron transfer from the ArOH molecule. Similarly, the second step of the SET-PT is a proton transfer from the resulting radical cation ($ArOH+\cdot$). For this reason, the ionization potential (*IP*) and proton dissociation enthalpy (*PDE*) values are the important parameters for the antioxidant reactivities.

The antioxidant compounds having the lower *IP* and *PDE* show the higher radical quenching effect.

$$\begin{aligned} R\cdot + ArOH &\rightarrow R^- + ArOH^+\cdot \\ R^- + ArOH^+\cdot &\rightarrow RH + ArO\cdot \end{aligned} \quad (3)$$

The third mechanism, the SPLET mechanism, is governed by proton affinity (*PA*) values, together with the electron transfer enthalpy (*ETE*) values of the phenoxide anion (ArO^-). The mentioned parameters can be also used to predict the antioxidant activities of the phenolic molecules.

$$\begin{aligned} ArOH &\rightarrow ArO^- + H^+ \\ R\cdot + ArO^- &\rightarrow R^- + ArO\cdot \\ R^- + H^+ &\rightarrow RH \end{aligned} \quad (4)$$

The aforementioned descriptors obtained from total enthalpy values at 298.15 K were calculated with the help of the following equations:

$$BDE = H_{ArO\cdot} + H_{H\cdot} - H_{ArOH} \quad (5)$$

$$IP = H_{ArOH^+\cdot} + H_{e^-} - H_{ArOH} \quad (6)$$

$$PDE = H_{ArO\cdot} + H_{H^+} - H_{ArOH^+\cdot} \quad (6)$$

$$PA = H_{ArO^-} + H_{H^+} - H_{ArOH} \quad (7)$$

$$ETE = H_{ArO\cdot} + H_{e^-} - H_{ArO^-} \quad (6)$$

The DFT computations were executed using Gaussian 16 [47] and GaussWiev 6 [48] programs. Becke B3LYP [49, 50] is a popular DFT hybrid function because it has low computational cost and more accuracy, and it is compatible with experimental results [51–56]. Additionally, B3LYP has good performance in geometry optimization and predicts the X–H bond energy [57–59]. Therefore, it was preferred in this study. B3LYP/6–311 + + G(d,p) level was used for the computations of neutral, anionic, cationic, and radical structures of the phenolic compounds. In addition, the spin densities for each atom of the radical molecules were obtained by NBO version 3.1 calculations at the same level of theory. The gas phase enthalpies of hydrogen atom, proton, and electron were used as 0.49765, 0.00236, and 0.00118 hartree, respectively [60, 61].

Molecular docking

The potential binding mode and the binding interaction of ferulic acid and cinnamic acid ligands with the antioxidant proteins which are urate oxidase (PDB ID: 1R4U) [62], proline-rich tyrosine kinase 2 (PDB ID: 3FZS) [63], glutathione reductase (PDB ID: 1GRS) [64] have been examined using Maestro 12.5, Schrödinger 2020–3 package program [65]. The 3D crystal structure of the mentioned proteins was retrieved from the protein data bank. These proteins obtained from the protein data bank are not ready directly for the use of docking calculations on them. Addition of hydrogens, assigning of the partial charges, and building the side chains along with the filling of missing loops are applied using the Protein Preparation module of Schrodinger Maestro 12.5 version. The water molecules beyond 3 Å of the binding site in the crystal structures are removed. The minimized energy of the protein structure was obtained using the OPLS3e force field at pH: 7.0. The ligands were prepared for molecular docking with LigPrep using the same force filed (pH: 7.0 ± 2.0). The receptor grid was generated by clicking on any atom of the ligand, and the default grid box was created. The grid box was set with 20 × 20 × 20 volumetric spacing for all investigated proteins. The coordinates were taken as x: 31.11, y: 26.98, and z: 38.13 for 1R4U, x: − 3.5, y: − 3.23, and z: 12.43 for 3FZS, x: 60.71, y: 51.38, and z: 18.86 for 3GRS.

ADME study

A set of ADME properties of the ferulic acid and the cinnamic acid were calculated using a QikProp tool in the Schrodinger program [66]. QikProp module generates relevant descriptions and uses them to carry out ADME estimations and uses the method of Jorgensen to obtain pharmacokinetic properties and descriptors.

Results and discussion

The TPC, TFC, and TAC investigations

The antioxidant properties of plants can be referred to the phenolic compounds due to their redox potentials that allow them to act as metal chelating, quenching of singlet oxygen, hydrogen donors, and reducing agents. These species which are called as secondary plant metabolites contribute to the antioxidant ability of plants [67–70]. Furthermore, phenols play a role in reducing the harmful effects of reactive oxygen species (ROS) radicals. Phenol scavenging activity is dependent on the position of the hydroxyl substituents on the aromatic ring of phenolic molecule [71, 72].

Folin-Ciocaltue technique was used to determine the TPC. TPC was calculated with a regression equation based on a standard curve using gallic acid at different concentration ($R^2 = 0.998$) and expressed as milligram of gallic acid equivalents per gram dry material, i.e., mg GAE g^{-1} DW. The phenolic concentration of methanolic extract of *A. virgatum* was determined as 161.25 mg GAE/g DW in Table 1.

Table 1 The experimental TPC, TFC, and TAC values of methanol extract of *A. virgatum* plant

Plant extract	TPC (mg gallic acid g^{-1} dry material)	TFC (mg quercetin g^{-1} dry material)	TAC (mM α-tocopherol acetate g^{-1} dry material)
Alyssum virgatum	161.25 ± 0.73^a	119.89 ± 1.02^b	94.92 ± 1.27^c

The values are mean of triplicates ± SD

Mean values followed by different superscripts

$^{a>b>c}$ indicate an important statistical difference ($p < 0.05$)

The results of TFC obtained in the quantitative analysis are given in Table 1. TFC was determined comparing with a calibration curve of quercetin at 0–50 mg L^{-1} ($R^2 = 0.996$) and then expressed in mg quercetin equivalents per gram dry material, i.e., mg QUE g^{-1} DW. From Table 1, the flavonoid content of A. *virgatum* is found as 119.89 mg QUE/g DW. The achieved results indicate that the phenolic equivalent of gallic acid content was higher than the flavonoid equivalent of quercetin content in *A. virgatum* ($p < 0.05$).

The total antioxidant capacity of the methanol extract of *A. virgatum* plant was determined by the phosphomolybdenum with using α-tocopherol as a standard. The α-tocopherol is an antioxidant species with chain-breaking properties which inhibits the spread of free radical reactions. Additionally, it is a significant vitamin which is soluble in fat [73]. The basic of the method depends on the formation of green-colored complex of phosphate/Mo(V) in acidic pH with the reduction of acidic Mo(VI) to Mo(V). The TAC was determined comparing with a calibration curve of α-tocopherol acetate at 100–500 mg L^{-1} ($R^2 = 0.995$). The obtained results were indicated as mM α-tocopherol acetate per gram dry material. The TAC value methanol extract of *A. virgatum* is presented in Table 1. From Table 1, it can be stated that the mentioned methanolic extract has a TAC of 94.92 mM α-tocopherol acetate per gram dry material. It should be indicated that there are statistical differences between the TPC, the TFC, and the TAC values ($p < 0.05$).

The scavenging activity of hydrogen peroxide and hydroxyl radical

The scavenging activity of the *A. virgatum* plant extract was analyzed by using hydroxyl radical (·OH) and hydrogen peroxide (H_2O_2). The H_2O_2 is not a free radical. However, it can form a radical by many oxidase enzymes such as superoxide dismutase. The scavenging activities of H_2O_2 of the plant extract and positive controls are shown in Table 2. Additionally, it is stated that the plant extract and positive controls have an observable maximum inhibition of between 85 and 95%. To make comparisons to *A. virgatum,* the natural antioxidants such as curcumin and synthetic antioxidant butylated hydroxytoluene (BHT) were used. The IC_{50} value of the methanol extract was analyzed as 29.24 mg mL^{-1} for H_2O_2 scavenging activity. The IC_{50} value (16.35 mg mL^{-1}) of curcumin was substantially lower than that (48.78 mg mL^{-1}) of BHT. These results show that curcumin has the strongest hydrogen peroxide scavenging activity among the investigated species. Ranking of H_2O_2 scavenging activity is *Curcumin* > *A. virgatum* > BHT ($p < 0.05$). It should be stated that *A. virgatum* is stronger H_2O_2 scavenger than BHT which is synthetic antioxidant.

Hydroxyl radical is an oxygen-containing chemical species, and it is the most reactive free radicals in biological cells, which causes lipid oxidation and huge biological damage [74]. All of the samples show inhibition of between 75 and 85%. Table 2 shows the hydroxyl scavenging activity of positive controls and the plant extract. The lower IC_{50} means better protective effect of the extracts against hydroxyl radical. The IC_{50} values of hydroxyl scavenging effect of curcumin and BHT are obtained as 19.21 and 52.78 μg mL^{-1}, respectively ($p < 0.05$). However, there are no statistical differences between the IC_{50} values of the *A. virgatum* and the BHT ($p \geq 0.05$). These results also indicate that curcumin has a stronger hydroxyl radical scavenger than the plant extract and BHT.

Table 2 The ROS scavenging activities of the mentioned plant extract and positive controls

Sample	Hydrogen peroxide H_2O_2 IC_{50} (mg mL^{-1})	Hydroxyl radicals (•OH) IC_{50} (μg mL^{-1})
Alyssum virgatum	29.24 ± 2.49^b	46.04 ± 3.95^b
BHT	48.78 ± 2.72^c	52.78 ± 3.18^b
Curcumin	16.35 ± 1.37^a	19.21 ± 1.84^a

The values are mean of triplicates ± SD

Mean values followed by different superscripts

$^{a>b>c}$ show a significant statistical difference ($p < 0.05$)

HAT mechanism

BDE values of the O–H bond is an important descriptor to interpret the HAT reaction. The lower BDE values mean the higher antioxidant activity. While cinnamic acid has one O–H bond which is in the carboxyl group, ferulic acid has two O–H which are in the hydroxyl and carboxyl groups. The BDE values for the mentioned compounds are calculated in the gas phase, and they are presented in Table 3. Referring to Table 3, it is seen that the BDE value of the cinnamic acid is calculated as 99.35 kcal mol^{-1}. The mentioned BDE values for hydroxyl and carboxyl groups of ferulic acid molecule are obtained as 88.22 and 99.19 kcal mol^{-1}, respectively. It is noticed from Table 3 that the studied BDE values of the ferulic acid are smaller than those of cinnamic acid. The lowest BDE of the O–H bond belongs to the OH in the hydroxyl group of ferulic acid. The low BDE value of

Table 3 The calculated BDE values (kcal mol^{-1}) of the cinnamic acid and ferulic acid at 25 °C in the gas at B3LYP/6–311 + + G(d,p) level

	BDE
Cinnamic acid	
OH (carboxyl) ferulic acid	99.35
OH (hydroxyl)	82.22
OH (carboxyl)	99.19

Table 4 The computed IP and PDE values (kcal mol^{-1}) of the studied molecules in vacuo at B3LYP/6–311 + + G(d,p) level

	IP	PDE
Cinnamic acid	197.80	216.05
OH (carboxyl) Ferulic acid	178.84	
OH (hydroxy)		217.89
OH (carboxyl)		234.85

Table 5 The obtained PA and ETE values (kcal mol^{-1}) of the mentioned compounds in the vacuum at the same level of theory

	PA	ETE
Cinnamic acid	334.68	79.17
OH (carboxyl) Ferulic acid		
OH (hydroxy)	327.77	68.96
OH (carboxyl)	336.46	77.23

the O–H bond in the hydroxyl group of ferulic acid can be explained by aromatic conjugation because it stabilizes the radical. For that reason, the mentioned O–H bond is broken easier. According to the BDE values of the examined molecules, it is clear that ferulic acid has better antioxidant property than cinnamic acid. In other words, it can be stated that ferulic acid exhibits the best antioxidant activity in the main phenolic components of *A. virgatum.*

SET–PT mechanism

The first step of SET-PT reactions is related to the IP value of the compound. The lower IP shows the easier the electron donating ability. The IP values of studied molecules are presented in Table 4. The order of the IPs is ferulic acid < cinnamic acid at the B3LYP method. Considering IP values, it can be seen that that electron donating ability of ferulic acid is better than cinnamic acid molecules. Therefore, it can be said that scavenging activity of ferulic acid is better than those of cinnamic acid. These results are compatible with BDE values in Table 3.

The second step in the SET-PT mechanism is concerned with PDE values of molecules. The lower PDE means the easier reaction. PDEs of molecules are given in Table 4. From Table 4, it is seen that the lowest PDE value in ferulic acid is close to that of cinnamic acid. When IP and PDE values of the studied phenolic compounds are considered together, it can be stated that ferulic acid has better antioxidant scavenging reactivity than cinnamic acid. The results of this mechanism are compatible with those of HAT reactions.

SPLET mechanism

The first step of SPLET mechanism is PA reaction. In this reaction, it is apparent that the compound with lower PA has higher proton affinity. The lower proton affinity purports the higher antioxidant activity. The PA values of the investigated molecules are shown in Table 5. It is apparent from Table 5 that ferulic acid, which has low PA exhibit better antioxidant properties than cinnamic acid. ETE reaction is the second step of SPLET. The molecule with lower ETE gives easier reaction. From Table 5, it is noticed that ferulic acid has the lowest ETE value. According to ETE reaction, the ferulic acid shows better radical scavenging ability than cinnamic acid. When PA and ETE values of the studied molecules are considered together, it can be noticed that ferulic acid has better antioxidant scavenging reactivity than cinnamic acid. The results of this mechanism are quite compatible with those of HAT and SPLET mechanisms.

Spin densities

Spin density is the electron density applied to free radicals. It is well-known that spin density is an important descriptor to characterize the stabilities of free radicals. The delocalization of higher unpaired electrons means the lower the energy of the radical. In other words, the molecule having higher delocalization occurs easily. To show spin densities of the molecules, free radicals are obtained by hydrogen abstraction of the OH. Then the natural bond analysis calculation of the formed free radical is performed. Using NBO analysis, the spin density distributions are achieved.

The spin density distributions of the cinnamic acid and the ferulic acid radical are obtained in the abovementioned way and shown in Fig. 2. Figure 2 shows that spin density distributions created by removing the H atom from the carboxyl group of cinnamic acid and ferulic acid are similar to each other. In these radicals, spin densities are delocalized around the carboxyl group because two electronegative oxygen atoms in the carboxyl group quite attract electrons. On the other hand, spin density distribution formed by removing the H atom from the hydroxyl group of the ferulic acid is delocalized on the whole molecule because an oxygen atom connected to the phenolic ring attracts fewer electrons than two oxygens. So, the spin electron density spreads over the entire molecule. This distribution can be clearly seen in Fig. 1. Therefore, it can be stated that best stable molecule is hydroxyl-ferulic acid radical. Consequently, it can be said that ferulic acid has a higher radical quenching effect than cinnamic acid.

Molecular docking study

The molecular docking studies are based on ligand-antioxidant protein interactions. In this article, the aforementioned proteins are preferred to evaluate the biological activities of the ferulic acid and the cinnamic acid. The docking

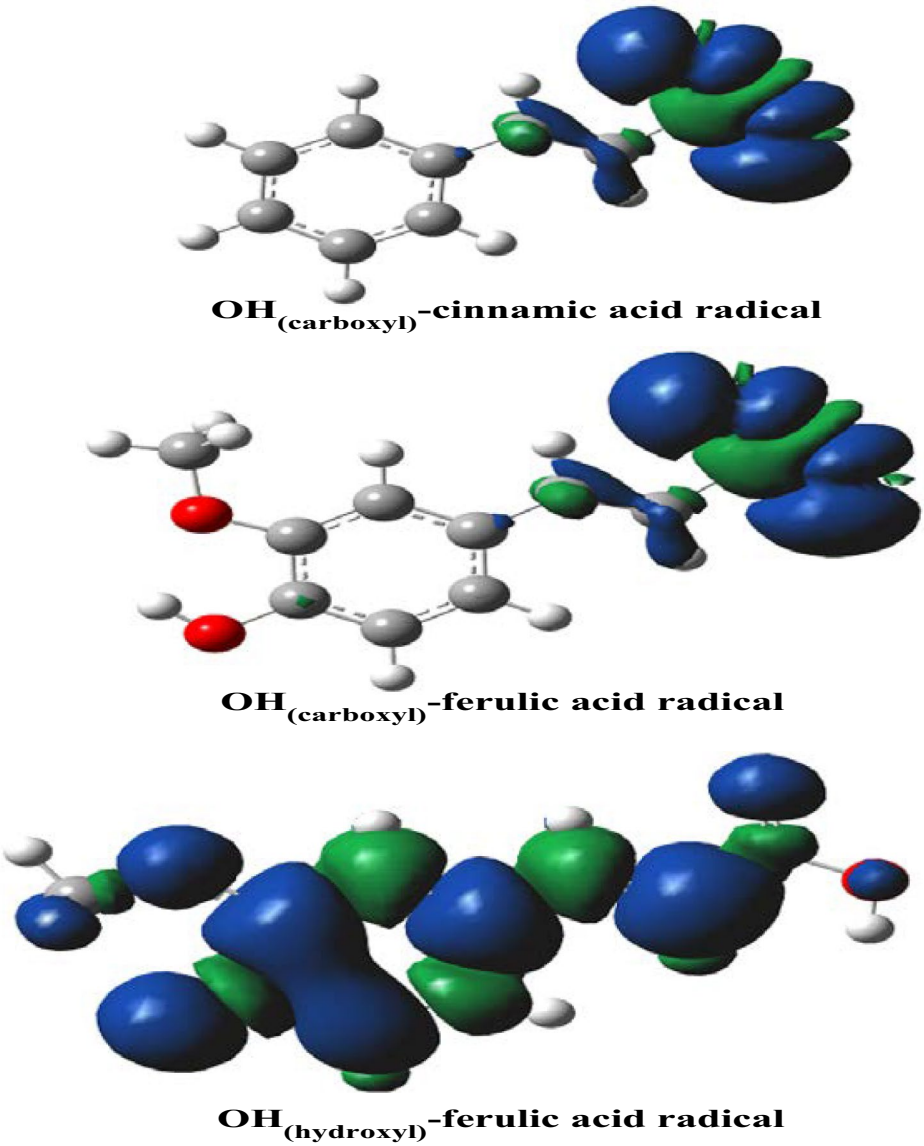

Fig. 2 The spin densities of the investigated molecules at B3LYP/6–311 + + G(d,p)

calculations of the ferulic acid and cinnamic acid ligands to the active site of the mentioned proteins are executed by Schrodinger program, Maestro 12.5 version. The pictorial demonstration (3D) and the ligand interaction diagram (2D) of the docked molecules are obtained as shown in Figs. 3 and 4, respectively.

As shown in Fig. 4, cinnamic acid in 1R4U forms hydrogen bonding with amino acid ARG 176 and the water molecule; ferulic acid in the same protein forms hydrogen bonding with ARG 166 and VAL 227. In 3FZS protein, while cinnamic acid forms salt bridge bonding with LYS 457, ferulic acid forms hydrogen bonding with GLU 464 and the water compound. Finally, cinnamic acid in 3GRS forms hydrogen bonding with amino acid GLY 31, ASP 331, and two water molecules; ferulic acid in the same enzyme forms hydrogen bonding with GLU 50, GLY 31, and three water compounds.

Besides aforementioned interactions, the significant parameters are achieved from interactions of the target protein with the mentioned ligands. Among these, the most important parameter is Docking score. The resulting docking results of the mentioned ligands are tabulated in Table 6. It is seen from Table 6 that the docking scores of cinnamic acid and ferulic acid are in the range of – 3.403 to – 5.921. According to the Docking scores, it is clear that biological activity of ferulic acid in investigated antioxidant proteins is higher than those of cinnamic acid. These data are compatible with the aforementioned DFT results. Also, it is indicated that ferulic acid shows the best activity in 3GRS enzyme.

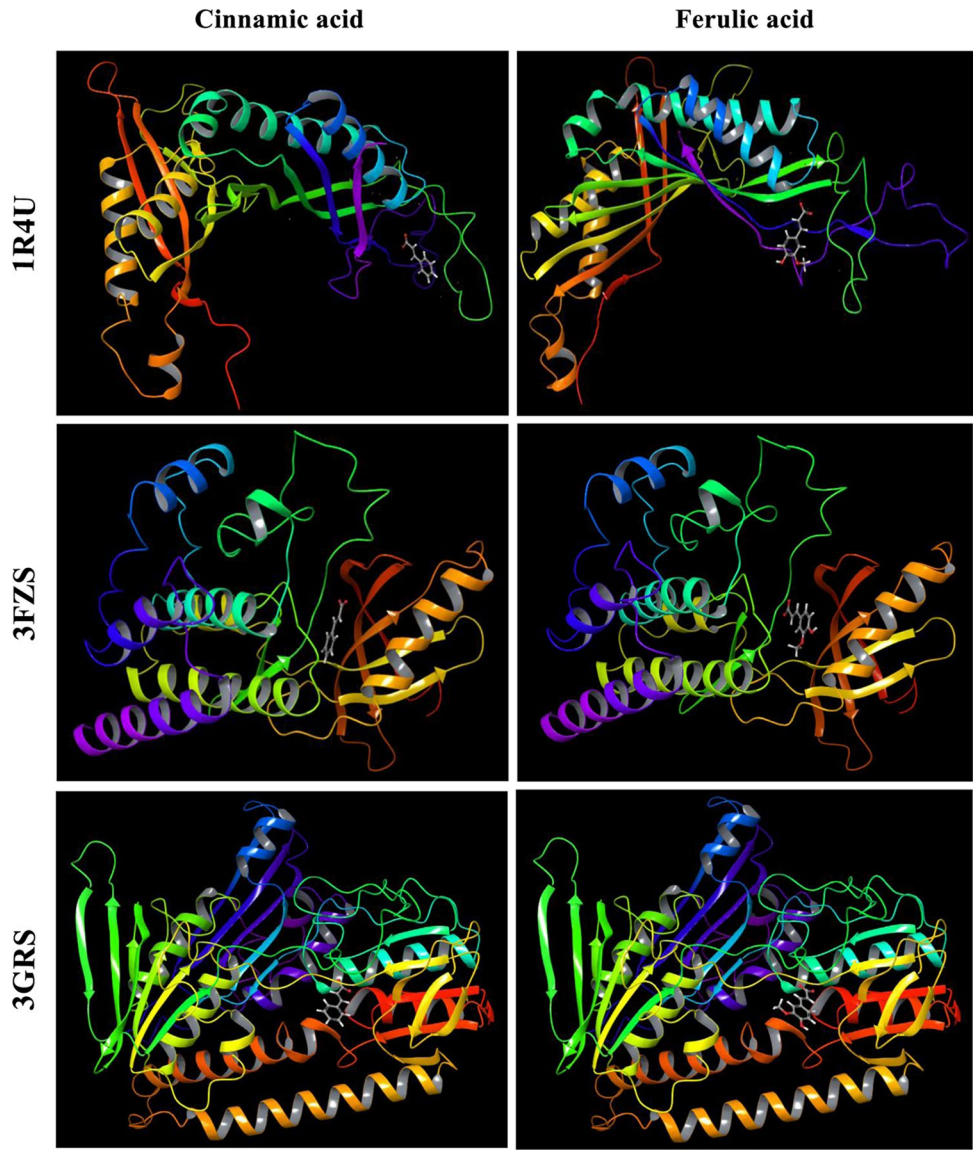

Fig. 3 3D demonstration of the docking of the mentioned antioxidant proteins with the ligands

Additionally, it is apparent that Glide energies of cinnamic acid are smaller than that of ferulic acid. According to these results, it can be said that the biological activity of ferulic acid is higher than that of cinnamic acid.

ADME analysis

The ADME properties of the examined ligands are determined in silico by using QikProp module of Schrodinger suite 2020–3. Some of the obtained ADME properties are given in Table 7. Referring to Table 7, the calculated dipole moment of cinnamic acid and ferulic acid are 6.700 and 6.384, respectively. While the predicted number of hydrogen bonds that would be donated by the solute to water compounds in an aqueous solution of the cinnamic acid and the ferulic acid is 1 and 2, the obtained number of hydrogen bonds that would be accepted by the solute to water compounds in an aqueous solution of the mentioned ligands is 2 and 3.5. Finally, it is noticed from Table 7 that % human oral absorption of the aforementioned ligands are in the range of 67–80%. According to the values, it can be said that almost all the ADME properties of the molecules are within the recommended values. Additionally, it is apparent from Table 7 that the drug activity of ferulic acid is higher than that of cinnamic acid. Consequently, it can be stated ferulic acid has better drug activity than that of cinnamic acid.

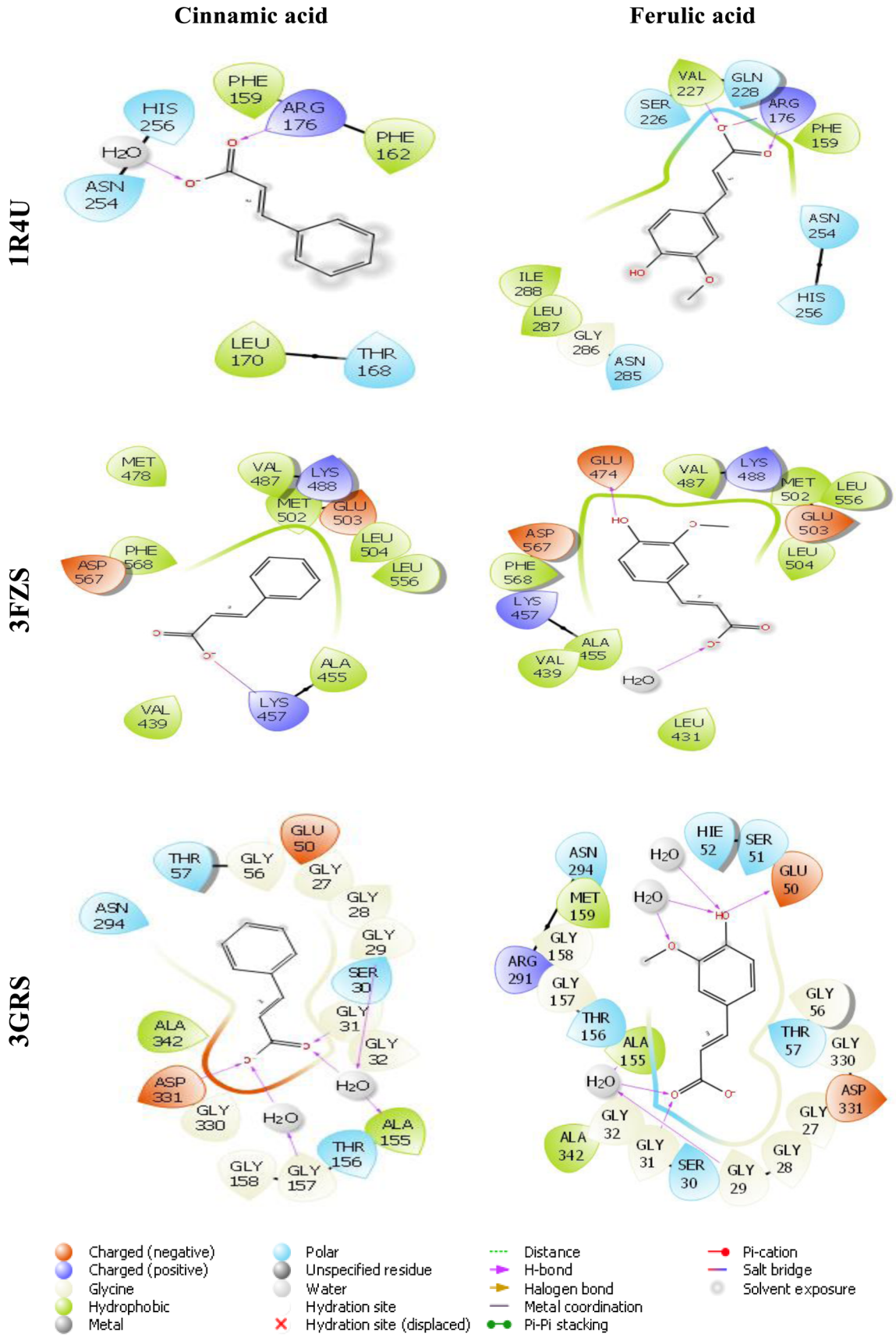

Fig. 4 2D presentation of the interaction between the receptor region of the target protein with the investigated molecules

Table 6 The docking results obtained from interaction of the ferulic acid and cinnamic acid with the mentioned proteins

Protein	Ligand	Docking score	Glide hbond	Glide emodel	Glide ligand efficiency	Glide energy
1R4U	Cinnamic acid	−3.403	−0.360	−23.118	−0.309	−15.916
	Ferulic acid	−5.244	−0.537	−32.627	−0.375	−20.450
3FZS	Cinnamic acid	−4.904	−0.015	−24.889	−0.446	−18.341
	Ferulic acid	−5.806	−0.160	−35.788	−0.415	−26.344
3GRS	Cinnamic acid	−4.795	−0.534	−45.589	−0.436	−31.345
	Ferulic acid	−5.921	−0.506	−56.333	−0.423	−36.562

Table 7 The ADME parameters of the mentioned ligands

Compound	Dipole	Mol MW	Donor HB	Accpt HB	QPlogPo/w	No. of meta	QPlogKhsa	Rule of Five	% Human oral absorption
Cinnamic acid	6.700	148.161	1	2	1.897	0	−0.518	0	79.497
Ferulic acid	6.384	194.187	2	3.5	1.371	2	−0.612	0	67.241
Recommended	1–12.5	130–725	0–6	2–20	−2–6.5	1–8	−1.5–1.5	Max 4	>80% is high <25% is poor

Conclusions

In the present study, it is determined that the methanolic plant extract has had rich content in terms of phenolic and flavonoid molecules. The phenolic compounds were higher than the flavonoid content in both experimental results and HPLC analyses.

The *A. virgatum* showed the scavenging activity of ROS. Curcumin was more effective than both the plant extract and positive control BHT at scavenging activity ROS. But the plant extract exhibited more scavenging activity than synthetic antioxidant BHT for hydrogen peroxide. However, there were no statistical differences between the values of the *A. virgatum* and the BHT at scavenging effect of hydroxyl radical.

The results of the present study indicate that methanol extracts of *A. virgatum* plant can be useful as an antioxidant source. For that reason, using this valuable strain in pharmaceutical products and food, their cultivation and conservation are of great importance. Further work is required involving isolation and purification of chemical compounds, so that the plants can be used as a natural antioxidant agent.

Cinnamic acid and ferulic acid, which are phenolic compounds are the main components of the *A. virgatum.* The antioxidant properties of the mentioned phenolic molecules can be explained by means of the HAT, SET-PT, SPLET mechanisms, and the spin density distributions which are investigated by DFT results. Based on the DFT study, it has been seen that ferulic acid is a better antioxidant than cinnamic acid.

The molecular docking studies of the antioxidant proteins with the main components are carried out. The docking results suggest that the biological activity of ferulic acid is better than cinnamic acid.

The in silico ADME predicts of the investigated molecules are calculated. From computed ADME properties, it is seen that the ferulic acid has better drug activity than the cinnamic acid.

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Data availability N/A.

Code availability GaussView 6.0, Gaussian 16, Schrodinger 2020–3.

Declarations

Conflict of interest The authors declare no competing interests.

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