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Molecular docking and A DFT study on the antiradical activity of naringenin and hesperetin with nitric oxide, peroxy, and methoxy radicals

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Abstract

Naturally occurring flavonoids, naringenin (N) and hesperetin (H), were theoretically investigated for their ability to scavenge nitric oxide, peroxy, and methoxy radicals in gas, water, and benzene solvent media. BMK/6-311+G(d,p) level of theory was used to for determine antiradical activity of the selected compounds and the calculation of reaction enthalpies related to three possible mechanisms of free radical scavenging activity, namely, hydrogen atom transfer (HAT), single electron transfer–proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET). When the results were examined, it was seen that the SET-PT mechanism was not an effective antioxidant effect mechanism in any solvent medium. In addition, in the absence of any radicals, HAT in the gas phase, SPLET in the water phase, and HAT and SPLET in the benzene phase are in competition. When the investigated antioxidants were examined in the presence of various radicals in terms of their antiradical scavenging properties, it was observed that the SET-PT mechanism was not possible in all radicals and all solvent phases due to positive ionization potential (IP) values. In addition, it was determined that the SPLET mechanism pathway was the most likely mechanism pathway with all the radicals examined. In addition, molecular docking calculations of the studied molecules were made to compare the activities against to human peroxiredoxin-5 (HP5), a protein with antioxidant properties.

KEYWORDS

DFT, flavonoids, hesperetin, naringenin, radical, reactive nitrogen species

1 | INTRODUCTION

Phenolic compounds are secondary metabolites of plants and are found in plants and fruits. The term phenolics generally consists of thousands of naturally occurring simple phenolics and polyphenols. Flavonoids (flavones, flavanones, flavonols, flavanols, anthocyans, etc.) constitute a subcategory of polypheneos. It is generally known that flavonoids have many human health benefits. In studies conducted, it has been determined that the consumption of foods and beverages containing high levels of polyphenolic compounds is highly correlated with the decrease in the incidence of osteoporosis, cardiovascular diseases, cancer, diabetes and neurodisease.[1–8] It is known that the antioxidant properties of flavonoids have an important effect on oxidative processes caused by reactive free radical species.[9]

The flavonols and their glycosides, the flavanols and the anthocyanins, are the predominant flavonoid classes found in fruit. The genus Citrus is characterized by a substantial accumulation of flavanone glycosides, which are not found in many other fruit, at the expense of the accumulation of flavanols and anthocyanins. Some of these flavanone and flavanolol compounds are intermediates in the biosynthetic pathways that lead from hydroxycinnamic acids and mal-onyl coenzyme A to anthocyanins, flavanones and flavonols. Each plant species is characterized by a particular flavanone glycoside pattern 2°. The flavanone aglycones are the 5,7-dihydroxy structures naringenin and hesperetin, and their 4′-methoxylated derivatives, isosakuranetin and hesperetin; the major glycosides are narirutin and hesperidin, the 7-rutinosides of naringenin and hesperetin. Lemon peel contains two flavanone glycosides, hesperedin and eriocitrin, the 7-rutinosides of hesperetin and eriodic- tyol, respectively. In grapefruit, naringin (the 7-neohesperidoside of naringenin) is predominant and is accompanied by narirutin (naringenin 7-rutinoside). Naringenin constitutes 88% (v/v) of flavanones in the juice. Naringin also predominates in the juice of sour orange (56–71%, v/v), along with other neohesperidosides - particularly the 7-neohesperido- side of eriodictyol (neoeriocitrin). Only the 7-∼-rutinosides are present in sweet orange, hesperidin being the dominant flavanone glycoside. In juice of sweet orange, hesperidin is accompanied by narirutin. Citrus fruits also contain several flavones, some of which are polymethoxylated flavones, such as nobiletin and sinensetin in orange peel (Table 1).[10]

Reactive nitrogen species (RNS) are types that contain radicals such as nitric acid (•NO) and nitric dioxide (NO_2), as well as non-radicals such as nitrous acid (HNO_2) and dinitrogen tetroxide (N_2O_4). Reactive nitrogen species (RNS) are very important due to the regulation of various biological processes in plant growth and development under stress conditions and normal growing conditions. Reactive nitrogen species (RNS) form free radicals and non-radical molecules under stress conditions, just like reactive oxygen species (ROS). Nitric oxide (•NO)is produced by many cells in the body, especially endothelial cells. Nitric oxide can also transform into many other radicals.[11–13]

Quantum chemistry is a powerful tool to theoretically predict the free radical scavenging capacities of the flavonoids. For this purpose, we evaluated by quantum chemical methods antioxidant action mechanisms of two flavanones: naringenin (N) and hesperetin (H) (see Scheme 1 for schematic representation).

The main objective of the present work is to perform a comprehensive study on the radical scavenging activity of naringenin (N) and hesperetin (H). All three probable mechanisms, that is, hydrogen atom transfer (HAT), single electron transfer–proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET) have been discussed in the gas, water and benzene phases. Subsequently, the activities of the molecules against Human peroxiredoxin 5 (HP5) (pdb ID: 1HD2) enzyme protein was examined. Human Peroxiredoxin-5 (HP5),[14] mitochondrial is a protein that in humans is encoded by the HP5 gene.

TABLE 1 Hierarchy of naringenin and hesperetin antioxidant activities and the relationship with reduction potentials

Flavonoid	Antioxidant activity[a] (nM)	Half peak reduction potential[b] (mV)
Naringenin	1.5	0.6
Hesperetin	1.4	0.4

[a]Measured as the TEAC (trolox equivalent antioxidant activity) the concentration of trolox with the equivalent antioxidant activity of a 1 mM concentration of the experimental substance.[10]

[b]Designated Ep/2. An Ep/2 of <0.2 indicates a chemical that is readily oxidized and therefore an efficient free radical scavenger.[10]

2 | COMPUTATIONAL DETAILS

Various quantum-mechanical approaches can be used to quantify the antioxidant activity.[15,16] In this study, GAUSSIAN 09 package program was used for molecular orbital studies.[17] As a result of the studies, it has been observed that the DFT model is very successful in determining molecular properties. Quantum chemical computational methods are a powerful method of supporting experimental data. As a result of the experiments,[18] in our study, Density Functional Theory method, BMK (Boese and Martin's τ-dependent hybrid functional) functional,[19] and the 6–311+G (d, p) basis set were chosen because of the high accuracy degree within Gaussian 09 package program.[20,21] When choosing the DFT method, many attempts were made first and the experimental bond dissociation enthalpy (BDE) values were compared with the data obtained as a result of the chosen method. As a result of this comparison, DFT method and the relevant basis set were studied as it was compatible with the experimental results. It was also confirmed by the literature review that the DFT method would be appropriate.[21] Optimized structures of selected antioxidant molecules and radicals are shown in Figure 1.

The solvation effect on the scavenging activities of investigated compounds was taken into account by using the conductor-like polarizable continuum model (C-PCM)[22] at the same level of theory.

SCHEME 1 Structures of naringenin and hesperetin

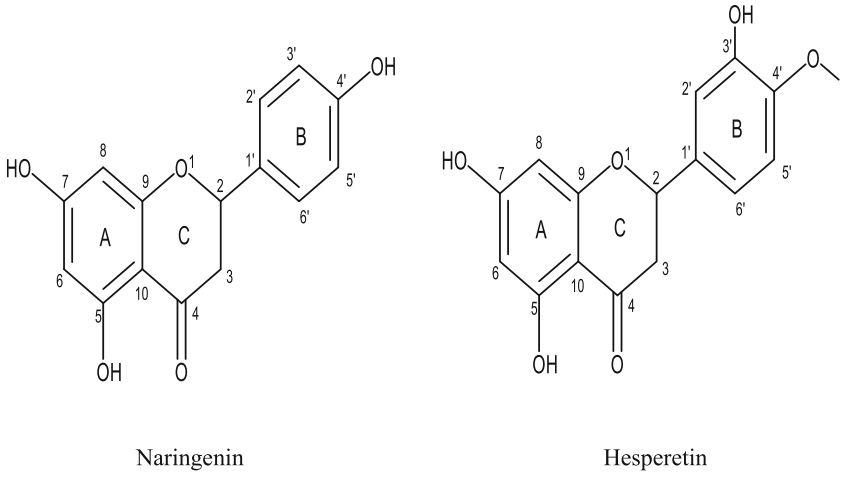
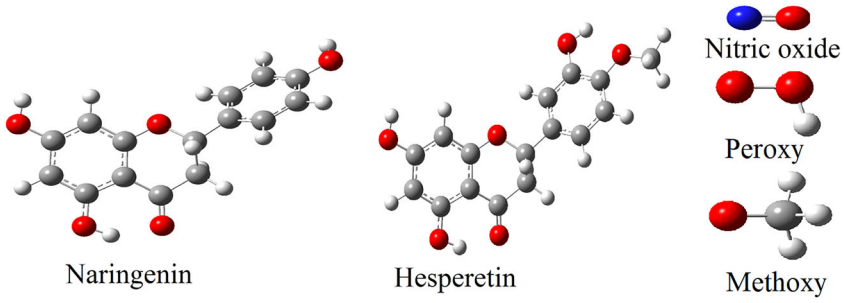


FIGURE 1 The optimized geometries of naringenin, hesperetin, nitric oxide, peroxy, and methoxy radicals



The reaction between the ROS and antioxidants can follow two different pathways: H-atom abstraction and radical adduct formation.[23,24] The first process will be investigated, and it includes mechanistic pathways that are considered to be different, but in essence, they are similar. It should be pointed out that the outcome of all discussed mechanisms is the formation of the more stable radical species, A-O•. Three different antioxidative mechanisms were studied and reported in this paper[25–30]: HAT, SET-PT, and SPLET. The transfer of hydrogen atom from the molecule of antioxidant to radical specie (Equation (1)) defines HAT mechanism. SET-PT is a two-step mechanism: the first step consists of the formation of radical-cation, which is the initial specie in the second step of this mechanism (Equations (2) and (3)). The other mechanism that consists of two-step reactions is the SPLET mechanism. Reactions that illustrate this mechanism are presented with Equations (4) and (5). The enthalpies of these processes can be used as the first parameter in the determination of the preferred mechanistic pathway of antioxidative reaction.

$$\mathrm{ArOH} \rightarrow \mathrm{ArO}\bullet + \mathrm{H}\bullet$$

$$\mathrm{ArOH} \rightarrow \mathrm{ArOH}^{+}\bullet + \mathrm{e}^{-}$$

$$\mathrm{ArOH}^{+}\bullet \rightarrow \mathrm{ArO}\bullet + \mathrm{H}^{+}$$

$$\mathrm{ArOH} \rightarrow \mathrm{ArO}^{-} + \mathrm{H}^{+}$$

$$\mathrm{ArO}^{-} \rightarrow \mathrm{ArO}\bullet + \mathrm{e}^{-}$$

The thermodynamic parameters that define these mechanisms are BDE for the HAT mechanism, IP (ionization potential) and PDE (proton dissociation enthalpy) for the SET-PT mechanism and PA (proton affinity) and ETE (electron transfer enthalpy) parameters for the SPLET mechanism. These parameters are calculated using the following equations.

$$\mathrm{BDE} = \mathrm{H}(\mathrm{ArO}^{\bullet}) + \mathrm{H}(\mathrm{H}\bullet) - \mathrm{H}(\mathrm{Ar-OH}) \quad (1)$$

$$\mathrm{IP} = \mathrm{H}(\mathrm{ArOH}^{+\bullet}) + \mathrm{H}(\mathrm{e}^{-}) - \mathrm{H}(\mathrm{Ar-OH}) \quad (2)$$

$$\mathrm{PDE} = \mathrm{H}(\mathrm{ArO}^{\bullet}) + \mathrm{H}(\mathrm{H}^{+}) - \mathrm{H}(\mathrm{ArOH}^{+\bullet}) \quad (3)$$

$$\mathrm{PA} = \mathrm{H}(\mathrm{ArO}^{-}) + \mathrm{H}(\mathrm{H}^{+}) - \mathrm{H}(\mathrm{ArOH}) \quad (4)$$

$$\mathrm{ETE} = \mathrm{H}(\mathrm{ArO}^{\cdot}) + \mathrm{H}(\mathrm{e}^{-}) - \mathrm{H}(\mathrm{ArO}^{-}) \quad (5)$$

The reaction of HAT, SET-PT, and SPLET mechanisms are also being followed when reaction includes free radical species (RO•). Reaction with reactive radical species,

that follows the HAT mechanistic pathway, is represented by Equation (6):

$$ArOH + RO\bullet \rightarrow ArO\bullet + ROH$$

SET-PT mechanism, the second of the radical scavenging ways, is a two-stage mechanism and is shown in Equations (7) and (8) below.

$$ArOH + RO\bullet \rightarrow ArOH^{+}\bullet + RO^{-}$$

$$ArOH^{+}\bullet + RO^{-} \rightarrow ArO\bullet + ROH$$

The third radical scavenging method is the SET-PT mechanism. This two-stage mechanism, the reactions of which are given below, is shown in Equations (9) and (10) below.

$$ArOH + RO^{-} \rightarrow ArO^{-} + ROH$$

$$ArO^{-} + RO\bullet \rightarrow ArO\bullet + RO^{-}$$

Radical scavenging with HAT mechanism (Equation (6)) is defined by the H-atom transfer from the examined compounds to the free radical species (RO•). ΔH_{BDE} can be calculated using the following equation:

$$\Delta H_{BDE} = H(ArO^{\bullet}) + H(ROH) - H(Ar-OH) - H(RO^{\bullet}) \quad (6)$$

The thermodynamic parameters of the SET-PT mechanism can be calculated by applying the following equation:

$$\Delta H_{IP} = H(ArOH^{+\bullet}) + H(RO^{-}) - H(Ar-OH) - H(RO^{\bullet}) \quad (7)$$

$$\Delta H_{PDE} = H(ArO^{\bullet}) + H(ROH) - H(ArOH^{+\bullet}) - H(RO^{-}) \quad (8)$$

The thermodynamic parameters (ΔH_{PA} and ΔH_{ETE}) of the SET-PT mechanism can be calculated using the following equations:

$$\Delta H_{PA} = H(ArO^{-}) + H(ROH) - H(ArOH) - H(RO^{-}) \quad (9)$$

$$\Delta H_{ETE} = H(ArO^{\cdot}) + H(RO^{-}) - H(ArO^{-}) - H(RO^{\cdot}) \quad (10)$$

The results for thermodynamic parameters of the studied reactions were obtained from vibrational frequency calculations at 298 K temperature.

A molecular docking study was carried out to investigate the antioxidant properties of the studied compounds. The molecular geometries of naringenin and hesperetin obtained from DFT calculations were used for the docking study. Molecular docking calculations have been made using important Human Peroxiredoxin-5 (HP5).

3 | RESULTS AND DISCUSSION

The formation of a stable phenoxyl radical after free radical scavenging is one of the most important indicators that phenolic compounds have antioxidative activity. The reaction enthalpies correlated to above-mentioned antioxidative mechanisms of naringenin and hesperetin (HAT, SET-PT, and SPLET) are calculated in gas, water, and benzene. The more appropriate antioxidant mechanism is determined by looking at the BDE, IP, and PA values.

Whichever of these values is the lowest indicates that it is the most thermodynamically preferred mechanism. The obtained values of thermodynamic parameters that describe antioxidant mechanisms of action are collected in Table 2. As a result of the calculations in gas, water and benzene phases, it is seen that the IP values calculated for the OH groups of naringenin and hesperetin are considerably higher than the BDE and PA values (Table 2). This result indicates that the SET-PT antioxidant action mechanism is not a possible mechanism of action in gas, water and benzene phases. When we examine the parameters of other mechanism paths, it is revealed that there are different situations in gas, water and benzene phases. When the results obtained for the BDE and PA values in the gas phase are examined, it is seen that the BDE values are quite low. When Table 2 is examined, it can be seen that the HAT mechanism, which has a low BDE value in the gas phase in the absence of any radical, is more likely. This result is compatible with the literature.[35]

In the water phase, when these two parameters are compared, it is revealed that the PA values are quite low. These results indicate SPLET mechanism as favorable mechanism of antioxidant action in water. When the results obtained were examined, it was determined that there was a different situation in the benzene phase. Namely, slightly lower values are achieved for BDE in benzene. Based on this fact, it could be said that probable mechanistic pathway of antioxidant action in benzene is HAT, but since PA values are not significantly higher

TABLE 2 BMK/6-311+G(d, p) BDE, IP, PDE, PA, and ETE values of naringenin and hesperetin in the gas phase, in water and in benzene (All values are in kcal·mol^{-1} energy unit). The enthalpies of hydrogen atom, proton and electron were taken from reference.[31–35]

	HAT			SET-PT						SPLET					
	BDE			IP			PDE			PA			ETE		
Antioxidant	Gas	Water	Benzene	Gas	Water	Benzene	Gas	Water	Benzene	Gas	Water	Benzene	Gas	Water	Benzene
Naringenin-4′	83.60	82.55	84.34	184.48	120.42	160.76	213.63	5.56	19.65	334.78	45.51	95.96	63.33	80.47	84.45
Naringenin-7	89.43	89.30	90.59	184.48	120.42	160.76	219.46	12.31	25.90	327.18	38.22	88.26	76.75	94.50	98.40
Naringenin-5	98.53	92.27	96.71	184.48	120.42	160.76	228.56	15.27	32.03	345.02	48.02	102.33	68.01	87.67	90.46
Hesperetin-3′	82.97	79.36	82.04	178.19	111.25	154.02	219.28	11.54	24.10	341.96	48.09	100.76	55.51	74.71	77.35
Hesperetin-7	89.19	89.04	111.35	178.19	111.25	154.02	225.51	21.22	53.41	327.97	38.21	88.81	75.73	94.26	118.62
Hesperetin-5	95.47	92.21	96.35	178.19	111.25	154.02	231.78	24.39	38.41	344.66	48.04	102.94	65.31	87.61	89.48

Abbreviations: BDE, bond dissociation enthalpy; ETE, electron transfer enthalpy; HAT, hydrogen atom transfer; IP, ionization potential; PA, proton affinity; PDE, proton dissociation enthalpy; SET-PT, single electron transfer–proton transfer; SPLET, sequential proton loss electron transfer.

than corresponding BDEs, the best is to conclude that HAT and SPLET are competitive in benzene. In addition, it should be pointed out that BDE and PA values obtained for naringenin and hesperetin are similar. This is a consequence of the structure of naringenin and hesperetin molecule (Figure 1). It is notable that methyl group have an insignificant contribution to the antioxidative properties due to its positive inductive effect.

Further is examined the radical scavenging activity in the presence of free radical species. It is known that the properties of the scavenged radical species greatly affect the scavenging mechanisms of antioxidants. Three different free radical species were used for calculations: nitric oxide radical (•NO), methoxy radical (CH3O•), and hydroperoxyl radical (•OOH).

The appropriate mechanism for the reactions of naringenin and hesperetin with selected free radicals is determined by examining the ΔH_{BDE}, ΔH_{IP}, and ΔH_{PA} values. More negative values indicate a thermodynamically favorable mechanism. Reaction enthalpy is a very important parameter in examining the processes between antioxidant species and free radicals. The enthalpy change of the reaction can be determined by subtracting the enthalpy of the reactants from the enthalpy of the products. If the new radical formed as a result of the reaction becomes more stable than the starting radical, the reaction becomes exothermic. This result indicates that this reaction route will be more suitable. Otherwise, if the newly formed radical is less stable than the starting radical, the reaction will be endothermic and this reaction path will not be suitable. When the enthalpy changes in Tables 3–5 are examined, it is seen that naringenin and hesperetin inactivate selected free radicals in all phases investigated by the appropriate antioxidant mechanism. First, it should emphasize that in both examined solvents and for all three examined free radical species are obtained positive values of ΔH_{IP}.

The results given in Tables 3–5 show that the SET-PT mechanism pathway is not a possible radical scavenging path in all cases investigated. The results show, that in gas, water and benzene •NO, •OOH, and CH_3O• radicals can be inactivated via SPLET. In addition, when the parameters obtained as a result of the reactions of •NO, •OOH, and CH_3O • with antioxidants are examined, it is revealed that the ΔH_{PA} value has much lower and negative values than the ΔH_{BDE} value in the gas, water, and benzene phase. Especially when Tables 3 and 4 are examined, we can see that the HAT mechanism is not suitable in the presence of OOH and NO radicals. As a result, all this shows that SPLET is the most appropriate antioxidant mechanism pathway to scavenge these three radicals.

TABLE 3 BMK/6-311+G (d, p) ΔH_{BDE}, ΔH_{IP}, ΔH_{PA}, ΔH_{PDE}, and ΔH_{ETE} values of the studied for the reaction of naringenin and hesperetin with the NO radical in the gas phase, in water and in benzene. (All values are in kcal/mol energy unit)

	HAT			SET-PT						SPLET					
	ΔH_{BDE}			ΔH_{IP}			ΔH_{PDE}			ΔH_{PA}			ΔH_{ETE}		
Antioxidant	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**
Naringenin-4′+NO	79.03	35.63	37.31	207.67	99.74	146.96	−128.64	−64.11	−109.65	−7.49	−24.2	−33.34	86.52	59.79	70.65
Naringenin-7+NO	84.86	42.37	43.56	207.67	99.74	146.96	−122.81	−57.36	−103.40	−15.09	−31.4	−41.04	99.95	73.82	84.60
Naringenin-5+NO	93.96	45.34	49.69	207.67	99.74	146.96	−113.71	−54.39	−97.27	2.75	−21.6	−26.98	91.21	66.99	76.66
Hesperetin-3′+NO	78.40	32.44	35.01	201.38	90.56	140.22	−122.99	−58.12	−105.20	−0.31	−21.58	−28.54	78.71	54.03	63.56
Hesperetin-7+NO	84.62	42.12	64.32	201.38	90.56	140.22	−116.76	−48.45	−75.89	−14.3	−31.45	−40.49	98.92	73.58	104.82
Hesperetin-5+NO	90.90	45.28	49.32	201.38	90.56	140.22	−110.48	−45.28	−90.90	2.39	−21.63	−26.36	88.51	66.92	75.68

Abbreviations: BDE, bond dissociation enthalpy; ETE, electron transfer enthalpy; HAT, hydrogen atom transfer; IP, ionization potential; PA, proton affinity; PDE, proton dissociation enthalpy; SET-PT, single electron transfer–proton transfer; SPLET, sequential proton loss electron transfer.

TABLE 4 BMK/6-311+G (d, p) ΔH_{BDE}, ΔH_{IP}, ΔH_{PA}, ΔH_{PDE}, and ΔH_{ETE} values of the studied for the reaction of naringenin and hesperetin with the OOH radical in the gas phase, in water and in benzene. (All values are in kcal/mol energy unit)

	HAT			SET-PT						SPLET					
	ΔH_{BDE}			ΔH_{IP}			ΔH_{PDE}			ΔH_{PA}			ΔH_{ETE}		
Antioxidant	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**
Naringenin-4′+OOH	1.52	0.43	0.99	162.91	51.32	100.25	−161.38	−50.89	−99.26	−40.24	−10.94	−22.95	41.76	11.37	23.94
Naringenin-7+OOH	7.35	7.18	7.24	162.91	51.32	100.25	−155.55	−44.14	−93.01	−47.83	−18.22	−30.65	55.18	25.40	37.89
Naringenin-5+OOH	16.45	10.15	13.36	162.91	51.32	100.25	−146.46	−41.17	−86.89	−29.99	−8.426	−16.59	46.44	18.57	29.95
Hesperetin-3′+OOH	0.89	−2.75	−1.31	156.62	42.15	93.51	−155.73	−44.91	−94.82	−33.06	−8.36	−18.16	33.94	5.61	16.85
Hesperetin-7+OOH	7.11	6.92	28.00	156.62	42.15	93.51	−149.51	−35.23	−65.51	−47.05	−18.24	−30.11	54.16	25.16	58.11
Hesperetin-5+OOH	13.39	10.09	13.00	156.62	42.15	93.51	−143.23	−32.05	−80.51	−30.36	−8.41	−15.97	43.74	18.51	28.97

Abbreviations: BDE, bond dissociation enthalpy; ETE, electron transfer enthalpy; HAT, hydrogen atom transfer; IP, ionization potential; PA, proton affinity; PDE, proton dissociation enthalpy; SET-PT, single electron transfer–proton transfer; SPLET, sequential proton loss electron transfer.

TABLE 5 BMK/6-311+G (d, p) ΔH_{BDE}, ΔH_{IP}, ΔH_{PA}, ΔH_{PDE}, and ΔH_{ETE} values of the studied for the reaction of naringenin and hesperetin with the OCH_3 radical in the gas phase, in water and in benzene. (All values are in kcal/mol energy unit)

	HAT			SET-PT						SPLET					
	ΔH_{BDE}			ΔH_{IP}			ΔH_{PDE}			ΔH_{PA}			ΔH_{ETE}		
Antioxidant	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**	**Gas**	**Water**	**Benzene**
Naringenin-4′ +OCH3	−15.78	−17.15	−16.37	152.20	45.15	92.51	−167.97	−62.29	−108.89	−46.83	−22.34	−32.58	31.05	5.20	16.21
Naringenin-7+OCH_3	−9.945	−10.40	−10.12	152.20	45.15	92.51	−162.14	−55.55	−102.64	−54.42	−29.63	−40.28	44.47	19.23	30.16
Naringenin-5+OCH_3	−0.85	−7.43	−4.00	152.20	45.15	92.51	−153.04	−52.58	−96.51	−36.58	−19.83	−26.22	35.73	12.40	22.22
Hesperetin-3′ +OCH_3	−16.41	−20.33	−18.67	145.91	35.98	85.77	−162.32	−56.3	−104.44	−39.65	−19.77	−27.78	23.23	−0.57	9.11
Hesperetin-7+OCH_3	−10.19	−10.65	−10.64	145.91	35.98	85.77	−156.09	−46.64	−75.13	−53.64	−29.64	−39.73	43.45	18.98	50.37
Hesperetin-5+OCH_3	−3.91	−7.49	−4.36	145.91	35.98	85.77	−149.82	−43.46	−90.13	−36.94	−19.81	−25.60	33.03	12.33	21.24

Abbreviations: BDE, bond dissociation enthalpy; ETE, electron transfer enthalpy; HAT, hydrogen atom transfer; IP, ionization potential; PA, proton affinity; PDE, proton dissociation enthalpy; SET-PT, single electron transfer–proton transfer; SPLET, sequential proton loss electron transfer.

A widely used method to compare the activities of molecules is molecular docking. The greater the interaction between the molecule and the protein, the greater the activity. The interactions between the protein and its studied molecule by the molecular docking method are shown in Figure 2. The human peroxiredoxin 5 (HP5) (pdb ID: 1HD2) protein was downloaded from the Protein Data Bank site for this comparison. The parameters obtained as a result of the calculations are given in Table 6. As a result of the calculations, the most important parameter showing the activity is the docking score. The more negative the numerical value of this parameter, the higher the activity of the molecule.[36,37] In addition to these parameters, Glide hbond, Glide evdw, and Glide ecoul parameters are also used to examine the interaction between molecule and protein. The numerical value of the Glide hbond parameter gives information about the number of hydrogen bonds formed during interactions. Glide evdw gives the numerical value of Van der Waals interactions between molecules and proteins. The glide ecoul parameter gives the numerical value of Coulomb interactions between molecules and proteins. Glide emodel, Glide energy, Glide einternal, and Glide posenum, which are numerical values related to the pose formed between molecules and proteins. The glide ligand activity parameter is a numerical value used to rank the activity of molecules.[38–40] The interactions of the molecules whose biological activity was calculated as a result of the calculations with the proteins are given in Figure 2.

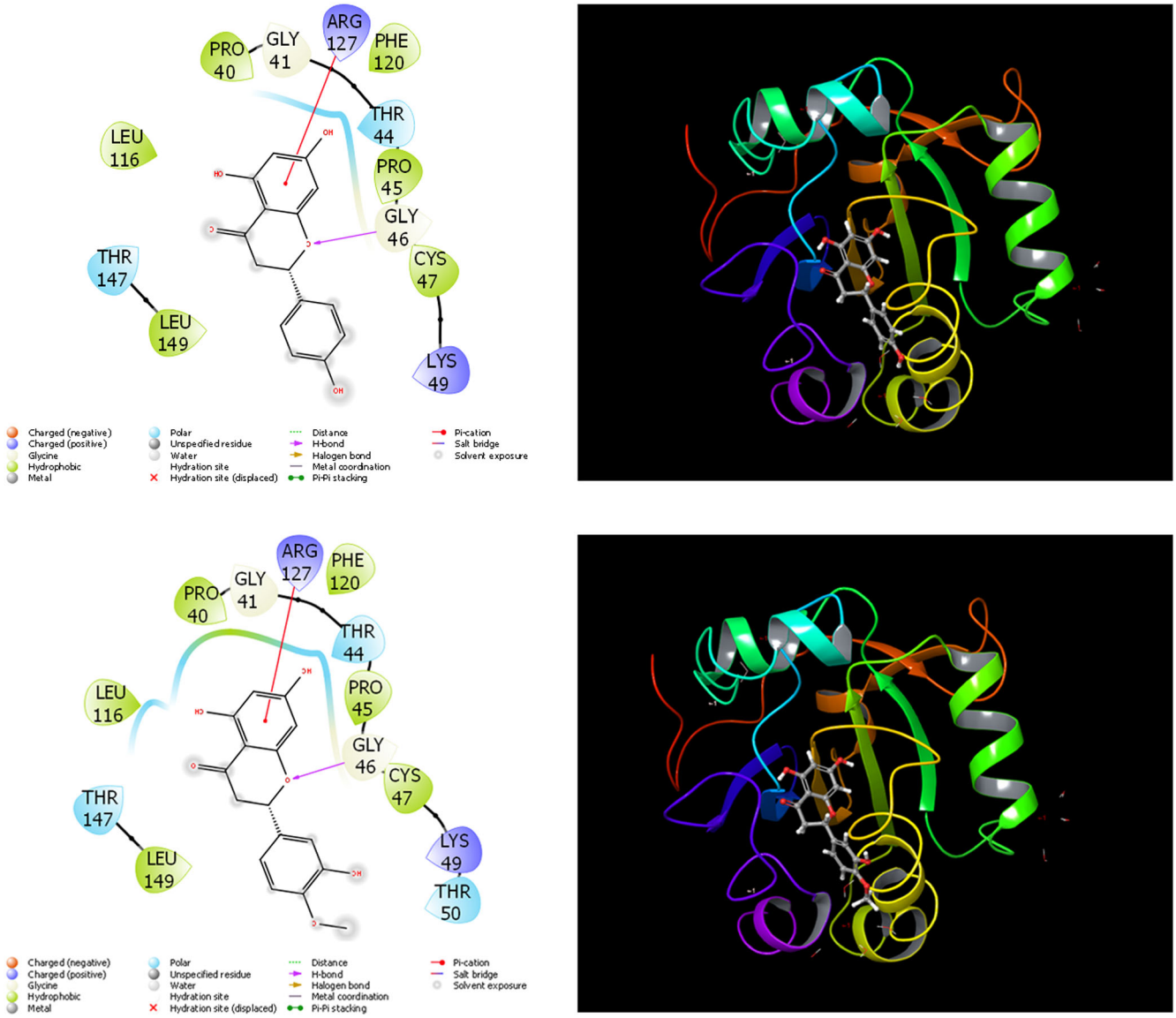


FIGURE 2 2D and 3D demonstration of interactions between of naringenin and hesperetin with HP 5 proteins

TABLE 6 Numerical values of the doking parameters obtained from interaction of studied molecules

Antioxidant	Docking score	Glide ligand efficiency	Glide hbond	Glide rewards	Glide evdw	Glide emodel	Glide energy	Glide einternal	Glide posenum
Naringenin	−5.29	−0.26	−0.65	−1.56	−9.30	−31.15	−23.15	0.12	261
Hesperetin	−5.56	−0.25	−0.61	−1.36	−10.11	−37.44	−26.65	0.35	209

4 | CONCLUSIONS

The antioxidative and inhibitory potency of naringenin and hesperetin are reported in the present study. The three antioxidative mechanisms of action were investigated. The thermodynamical calculations were performed in gas, water and benzene. The most probable antioxidant mechanism of action was determined by calculating the thermodynamic parameters and reaction enthalpies. The antioxidant effect was investigated in the absence of free radical species and in the presence of nitric oxide (•NO), methoxy (CH3O•), and hydroperoxyl (•OOH) radicals. As a result of the study, it is seen that the possible mechanism changes according to the ambient conditions and the presence or absence of radicals. When the ambient conditions are examined, it is determined that the possible antioxidant effect mechanism in gas is HAT, the possible mechanism in water is SPLET, and the possible mechanisms in benzene are HAT and SPLET as competitive mechanisms in the absence of free radical species (Table 2). SPLET was the only possible scavenging mechanism for naringenin and hesperetin in the presence of nitric oxide (•NO), methoxy (CH3O•), and hydroperoxyl (•OOH) radicals (Tables 3–5). These results were found to be in agreement with previous studies on this subject.[35,41] In addition, when all the results in our study were examined, it was seen that the antiradical properties of narengenin and hesperidin molecules were quite close to each other, which was consistent with the experimental results.[10] It is seen that the docking score of NAR and HES molecules are negative and they have very close activity to each other in Table 6. This result is in good agreement with other calculations and experimental results.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

CONSENT TO PARTICIPATE

Not applicable.

CONSENT TO PUBLISH

Not applicable.

AUTHOR CONTRİBUTIONS

Şaban Erdoğan and Dilara Özbakır Işın performed the calculations. Şaban Erdoğan and Dilara Özbakır Işın discussed and analyzed the results. All authors equally contributed to preparation of the manuscript. All the authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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