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ORIGINAL PAPER

Fisetin and Robinetin antiradical activity under solvent effect: density functional theory study

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Abstract

The structural and antioxidant activity of two flavonols, namely, Fisetin and Robinetin, have been investigated employing the density functional theory (DFT) using B3LYP functional and 6–311++G (d, p) basis set. The calculations were performed in the gas phase and under the solvent effect of water, dimethylsulfoxide (DMSO), methanol, and benzene. The Hydrogen-Atom Transfer (HAT), single Electron Transfer Followed by Proton Transfer (SET-PT), and sequential Proton Loss Electron Transfer (SPLET) mechanisms were investigated to rationalize the radical scavenging capacities and to identify the favored antioxidant mechanism. Hence, the bond dissociation enthalpies (BDE) ionization potential (IP), IE, proton dissociation enthalpy (PDE), proton affinity (PA), and electron Transfer enthalpy (ETE) related to each mechanism were reported and discussed in function of the solvent effect. For both flavonols, the results showed that 4′-OH hydroxyl is the preferred active site following the trend 4′-OH > 3′-OH > 3-OH > (5′-OH) > 7-OH. Besides, the HAT mechanism is energetically the most favored pathway. The energetically favored solvents follow the trends water > DMSO > benzene > methanol and benzene > DMSO > methanol > water, for Fisetin and Robinetin, respectively.

Keywords Fisetin · Robinetin · DFT · Antioxidant activity · HAT · SET-PT · SPLET · Solvent effect

Introduction

Flavonoid compounds were discovered in 1936 by the Hungarian Nobel laureate Albert Szent-Györgyi [1]. They are omnipresent in green plant cells and, therefore, expected to take part in the photosynthetic process [2]. Since their discovery, the study of these compounds has drastically increased, mainly because of their health benefits [3–5]. Flavonoids are mainly found in fruits, vegetables, propolis, and honey; they represent a common constituent of the human diet [2, 6–10]. Nutritionists estimate the average human intake of flavonoids on a normal diet by 203.0 ± 243.2 mg/day, with mostly quercetin and kaempferol [11–13]. The flavonoids' structure is composed of two aromatic rings denoted A, B connected through three carbons in an oxygenated heterocycle supplement. Multiple groups could be

Highlights

- The antioxidant activity of Fisetin and Robinetin compounds was theoretically rationalized under gas phase and solvent effect of water, dimethylsulfoxide (DMSO), methanol, and benzene at B3LYP/6-311++G(d, p) level of theory.
- The fundamental mechanisms related to the antioxidant activity: hydrogen-atom transfer (HAT), single electron transfer followed by proton transfer (SET-PT), and Sequential Proton Loss Electron Transfer (SPLET), were investigated. It was found that the HAT mechanism is thermodynamically the most favored pathway.
- The favorable active hydroxyls associated with the antioxidant activity follow the trend 4′-OH > 3′-OH > 3-OH > (5′-OH) > 7-OH.
- The energetically favored solvents follow the trends water > DMSO > benzene > methanol and benzene > DMSO > methanol > water for Fisetin and Robinetin, respectively.

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attached to the core structure, commonly hydroxyl, methoxy groups, and sugar. Differences in the structure of the heterocycle (C ring) classify them as flavonols, flavones, flavanols, flavanones, and isoflavones (Fig. 1). Flavonols are characterized by a 2, 3-double bond, a 4-keto group, and a 3-hydroxyl group in the C-ring. The flavonol structures of Fisetin and Robinetin are depicted in Fig. 2.

Flavonoid compounds have various properties including the antiradical activity or free radical scavenging property [14, 15], anti-cancer [16–18], the control of cellular growth [19–21], the destruction of pathogen organisms [22, 23], and the inhibition of human immunodeficiency viruses [24, 25]. Fisetin has been found in plants like *Arbutus unedo* L. [26, 27]; it is also abundant in strawberries and in some other fruits and vegetables [28]; and it has several biological activities such anticancer activity [29] anti-inflammatory [30], anti-HIV [31], and enhances memory [32]. Robinetin which has been isolated from *Intsia bijuga* plant [33] showed a powerful inhibitory action on lipid peroxidation [28].

Flavonoid compounds including Fisetin and Robinetin have various biological activities but their ability to scavenge free radicals is still the most interesting [28, 34, 35].

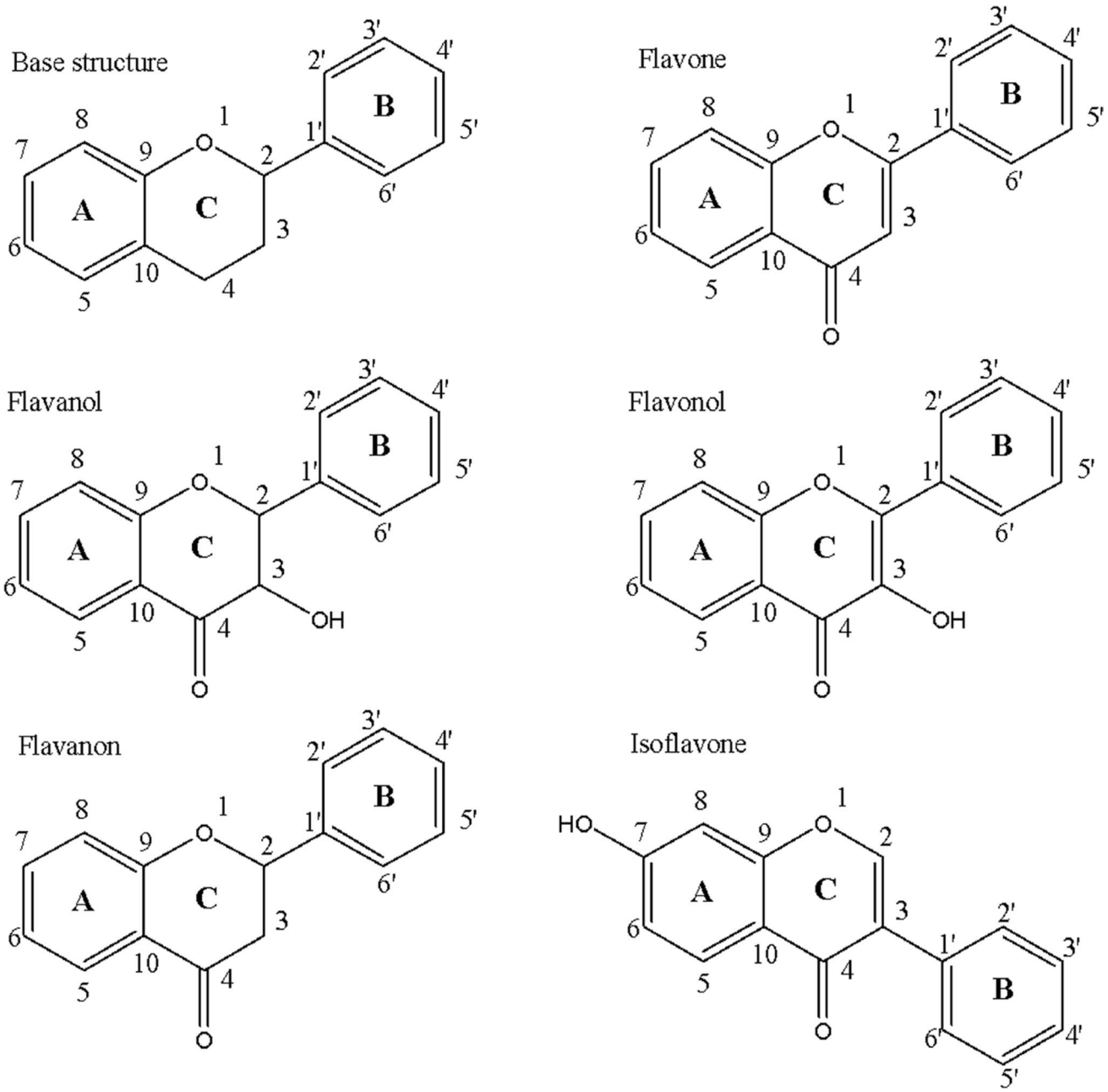

Fig. 1 Structures of flavonols, flavones, flavanols, flavanones, and isoflavones

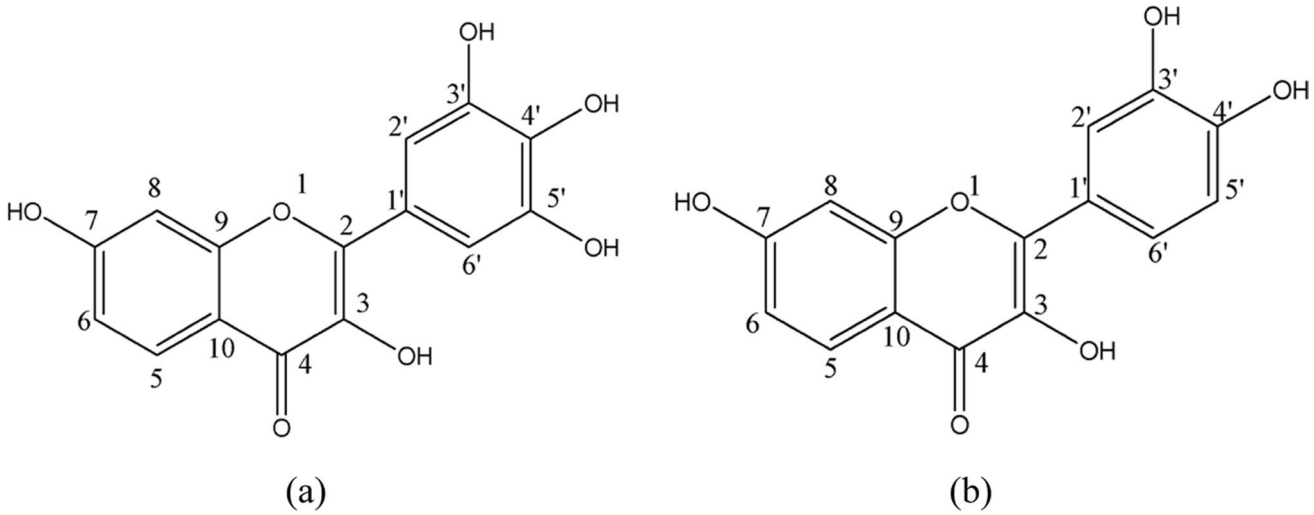

Fig. 2 **a** Robinetin and **b** Fisetin structures

These free radicals are dangerous and can damage biomolecules such as proteins, membrane lipids, and nucleic acids [36, 37]; thus, they are involved in several diseases [38]. Fisetin [39–47] and Robinetin [47–49] have been reported for their antiradical activity but the solvent effect on this activity is investigated in details here for the first time.

Therefore, in this study, we report the antiradical activity of Fisetin and Robinetin by the use of density functional theory (DFT) applying the most known mechanisms: hydrogen-atom transfer (HAT), single Electron Transfer followed by Proton Transfer (SET-PT), and sequential Proton Loss Electron Transfer (SPLET) [50–52], together with the solvent effect of polar, non-polar, protic, and aprotic solvents: benzene, DMSO, methanol, and water.

Theoretical and computational methods

The geometries of neutral molecules and the related species were firstly preoptimized by the PM7 semiempirical method as implemented in MOPAC2009 [53]. DFT calculations of optimization and vibrational frequencies were performed using B3LYP functional [54–56]; the exchange–correlation functional level was used without constraints, employing the 6–311 + + G(d,p) basis set [57–59] using Gaussian09 software [60]. The B3LYP level of theory is commonly used for organic molecule property calculations, especially the antiradical properties of flavonoids and nanostructures derived from them [61–65]. The solvents' effect was computed by DFT in the framework of the self-consistent reaction field polarizable continuum model (SCRF-PCM) [66–68], using the UAHF [69] set of solvation radii to build the cavity for the solute in its gas-phase equilibrium geometry. As implemented in Gaussian09 software to mimic experimental conditions, the following dielectric constants were used; $\varepsilon = 78.3553$ was chosen to perform calculations in water solution, $\varepsilon = 2.2706$ for benzene, $\varepsilon = 46.826$ for dimethylsulfoxide (DMSO), and $\varepsilon = 32.613$ for methanol.

The harmful action of free radicals ($R^{\cdot}$) can be avoided by scavenging them with flavonoids (FlOH) as shown in reaction (1):

$$FlOH + R^{\bullet} \rightarrow FlO^{\bullet} + RH \quad (1)$$

The product of this reaction is flavonoid phenoxyl radical (Fl–O$^{\bullet}$). A higher stability of the radical (Fl–O$^{\bullet}$) corresponds to a better efficiency of the antioxidant (Fl–OH). It is assumed that the resonance makes (Fl–O$^{\bullet}$) non-reactive (or less harmful) [70].

This reaction could happen through at least three mechanisms [71, 72]:

a- The hydrogen-atom transfer (HAT) as shown in reaction 2: this mechanism is characterized by the homolytic bond dissociation enthalpy (BDE) of OH group calculated as shown in Eq. 3

$$FlOH \rightarrow FlO^{\bullet} + H^{\bullet} \quad (2)$$

$$\mathrm{BDE} = H(\mathrm{FlO}^{\bullet}) + H(\mathrm{H}^{\bullet}) - H(\mathrm{FlOH}) \quad (3)$$

H(Fl-O$^{\bullet}$) is the enthalpy of the flavonoid phenoxyl radical generated after H abstraction, H(H) is the enthalpy of the hydrogen atom, and H(Fl–OH) is the enthalpy of the parent flavonoid molecule. A lower BDE value, usually related to a greater ability to donate a hydrogen atom from the hydroxyl group, results in an easier free radical scavenging reaction [40].

b- The single Electron Transfer followed by Proton Transfer (SET-PT): this mechanism occurs via two steps, starting from a single Electron Transfer characterized by the ionization potential (IP) as shown in reaction 4 and Eq. 5, respectively.

$$FlOH \rightarrow FlOH^{\bullet+} + e^{-} \tag{4}$$

$$\mathrm{IP} = H\left(\mathrm{FlOH}^{+\bullet}\right) + H(\mathrm{e}^{-}) - H(\mathrm{FlOH}) \tag{5}$$

The second step is characterized by a Proton Transfer as a proton dissociation enthalpy (PDE) as shown in reaction 6 and equation 7, respectively.

$$FlOH^{\bullet+} \rightarrow FlO^{\bullet} + H^{+} \tag{6}$$

$$\mathrm{PDE} = H(\mathrm{FlO}^{\bullet}) + H\left(\mathrm{H}^{+}\right) - H\left(\mathrm{FlOH}^{\bullet+}\right) \tag{7}$$

c- The sequential Proton Loss Electron Transfer (SPLET): this mechanism has two steps, starting from a deprotonation characterized by the proton affinity (PA) as shown in reaction 8 and Eq. 9, respectively.

$$FlOH \rightarrow FlO^{-} + H^{+} \tag{8}$$

$$\mathrm{PA} = H(\mathrm{FlO}^{-}) + H\left(\mathrm{H}^{+}\right) - H(\mathrm{FlOH}) \tag{9}$$

The second step consists of an electron Transfer characterized by the electron Transfer enthalpy (ETE) as shown in reaction 10 and equation 10, respectively.

$$FlO^{-} \rightarrow FlO^{\bullet} + e^{-} \tag{10}$$

$$\mathrm{ETE} = H(\mathrm{FlO}^{\bullet}) + H(\mathrm{e}^{-}) - H(\mathrm{FlO}^{-}) \tag{11}$$

Starting from neutral Fisetin in the gas phase, an H-atom is removed from the 7-OH position, giving rise to the 7-O$^{\bullet}$ radical. Likewise, 3-O$^{\bullet}$, 4′-O$^{\bullet}$, and 3′-O$^{\bullet}$ radical species (four radicals) are generated (Fig. 2). Then, each neutral structure and radical species was optimized under B3LYP/6–311++G (d, p) theory level in gas phase, water, benzene, and DMSO. Thus, the generated radical species generated from Robinetin were assigned as 7-O$^{\bullet}$, 3-O$^{\bullet}$, 3′-O$^{\bullet}$, 4′-O$^{\bullet}$, and 5′-O$^{\bullet}$. All the calculations were performed at 298.15 K.

DFT-based reactivity descriptors

According to Koopman's theorem [73], the following DFT-based descriptors are defined as follows:

The First Ionization Energy (I) and the Highest Occupied Molecular Orbital energy (E_{HOMO})

$$I \approx -E_{HOMO} \tag{12}$$

The electron Affinity (A) and the lowest Unoccupied Molecular Orbital Energy (E_{LUMO})

$$A \approx -E_{LUMO} \tag{13}$$

$$\Delta E_{gap} = E_{LUMO} - E_{HOMO} \tag{14}$$

$$\mu = -x \tag{15}$$

where μ is the chemical potential, and χ is the electro-negativity.

Using a finite difference approximation and Koopmans's theorem, the above expressions can be written as follows:

$$\text{The chemical potential } \mu: \mu \approx \frac{1}{2}(E_{LUMO} + E_{HOMO}) \tag{16}$$

$$\text{The global hardness } \eta: \eta \approx \frac{1}{2}(E_{LUMO} - E_{HOMO}) \tag{17}$$

$$\text{The global softness } S: S = \frac{1}{\eta} \tag{18}$$

$$\text{The electrophilic index } \omega: \omega = \frac{\mu^2}{2\eta} \tag{19}$$

Results and discussion

HOMO–LUMO energy gaps

Figure 3 depicts the optimized geometries and the frontier orbitals HOMO and LUMO of Fisetin and Robinetin at B3LYP/6–311++G(d,p) theory level in gas phase.

HOMO and LUMO magnitudes are directly associated with the ability of the molecule to donate electrons and to accept electrons, respectively. Moreover, large HOMO–LUMO gap energy (E_{gap}) indicates a high molecular stability; in contrast, a small gap energy indicates a high chemical reactivity. The values of HOMO, LUMO, and their related energy gaps are shown in Table 1. The E_{gap} changes slightly in the gas phase, E_{gap} of Fisetin is calculated as 3.931 eV, whereas the E_{gap} for Robinetin is 3.932 eV. Robinetin has the lowest E_{gap} values 3.676, 3.701, and 3.648 eV; in contrast, Fisetin has the following E_{gap} values 3.938, 3.950, and 3.912 eV in benzene, DMSO, and water, respectively. In contrast, Fisetin has shown (Fig. 4) in methanol lower E_{gap} value (3.753 eV) compared to Robinetin E_{gap} (3.843 eV). These E_{gap} values are in the

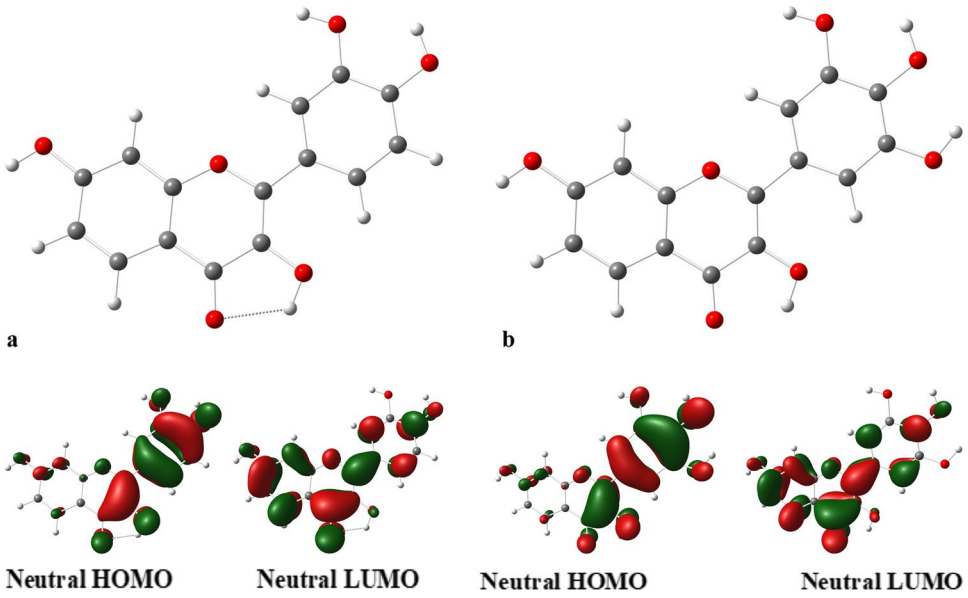

Fig. 3 The optimized geometries of (**a**) Fisetin and (**b**) Robinetin at B3LYP/6–311++G(d, p) theory level in gas phase

Table 1 HOMO, LUMO, and gap energies (eV/molecule) of Fisetin and Robinetin at B3LYP/6–311++G(d,p) in the gas phase, water benzene, and DMSO solvents

	Energy (eV)	Gas phase	Benzene	DMSO	Methanol	Water
Fisetin	HOMO	−6.2243	−6.1645	−6.1419	−5.9473	−6.1805
	LUMO	−2.2934	−2.2267	−2.1913	−2.1946	−2.2686
	Gap	3.9310	3.9378	3.9505	3.7527	3.9119
Robinetin	HOMO	−6.2755	−5.8464	−5.8722	−6.0793	−5.8534
	LUMO	−2.3437	−2.1698	−2.1709	−2.2354	−2.2049
	Gap	3.9318	3.6765	3.7013	3.8439	3.6485

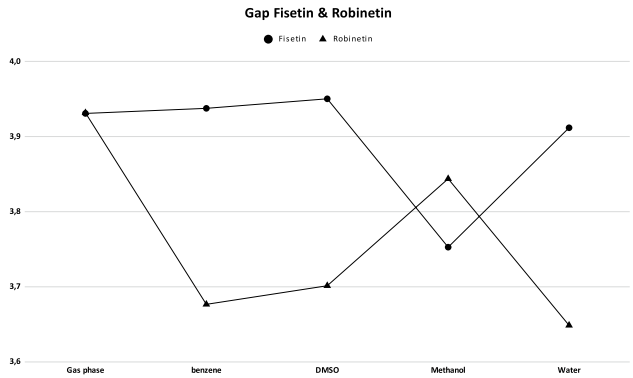

Fig. 4 Gap energy values of Fisetin and Robinetin in eV/molecule

Table 2 DFT-based reactivity descriptors: ionization potential (IP), electronic affinity (EA), chemical potential (μ), electronegativity (χ), hardness (η), softness (S), and the electrophilic index evaluation (w) for Fisetin and Robinotin at B3LYP/6–31++G(d, p) theory level in water in eV

Parameter	Fisetin	Robinetin
Ionization potential (IP)	6.1805	5.8534
Electronic affinity (EA)	2.2686	2.2049
Electro-negativity (χ)	4.0965	4.0666
chemical potential (μ)	−4.0965	−4.0666
Hardness (η)	1.8815	1.8470
Softness (S)	0.5315	0.5414
Electrophilic index (w)	4.4596	4.4769

same range as previous works which adopted the same level of theory and different basis sets [49, 74–76].

To evaluate the antioxidant properties of Fisetin and Robinetin, it is important to analyze the DFT-based reactivity descriptors, especially the chemical hardness, chemical softness, and the ionization potential (Table 2). The chemical hardness is a measure of resistance to charge transfer; it is remarkable that there is a slight reduction in the magnitude of hardness of Robinetin (1.8470 eV) compared to Fisetin (1.8815 eV). Consequently, the magnitude of softness of Robinetin (0.5414 eV) is greater than that of Fisetin (0.5315 eV). Electronegativity is a measure of the tendency to attract electrons. It is observed that the IP value of Robinetin (5.8534 eV) is lesser than Fisetin (6.1805 eV), which indicates that electron donating capability of Robinetin is higher than that of Fisetin. The calculated molecular properties clearly confirm that Robinetin acts as an electron donor rather than electron acceptor better than Fisetin.

BDE, IP, PDE, PA, and ETE energies

Flavonoid compounds have the capability to protect cells from oxidative stress by scavenging the free radicals either by donating an H-atom. It is well known that the easiest homolytic cleavage of an O–H bond (BDE_{min}, $(IP+PDE)_{min}$, and $(PA+ETE)_{min}$) indicates specifically the most favorable radical for the antioxidant activity.

Tables 3 and 4 show the computed thermodynamic parameters BDE, IE, PDE, PA, and ETE associated with the

Table 3 Fisetin IP, BDE, PDE, PA, and ETE energy values in kJ/mol

	Fisetin	Gas phase	Benzene	DMSO	Methanol	Water
IP		2.654	593.43	449.58	450.56	429.45
BDE	3-OH	338.20	335.98	320.92	325.80	319.01
	3′-OH	307.46	313.90	312.56	316.08	310.37
	4′-OH	**296.46**	**302.53**	**300.73**	**304.72**	**299.13**
	7-OH	347.50	352.15	348.27	360.59	354.58
PDE	3-OH	44.37	154.28	− 10.11	63.15	78.92
	3′-OH	95.70	132.20	− 18.47	53.44	70.29
	4′-OH	19.19	120.83	− 30.30	42.07	59.05
	7-OH	31.73	170.46	17.24	97.94	114.50
PA	3-OH	1368.98	430.25	127.59	147.90	181.16
	3′-OH	1420.31	385.27	94.99	173.51	156.61
	4′-OH	1343.80	365.24	80.70	137.32	146.87
	7-OH	1356.34	375.95	92.26	153.35	163.18
ETE	3-OH	296.97	317.46	311.88	365.81	327.21
	3′-OH	214.90	340.35	336.12	330.49	343.12
	4′-OH	280.41	349.02	338.59	355.31	341.62
	7-OH	318.91	387.93	374.56	395.14	380.77

The values in bold typeface indicate the lowest value for a given solvent

Table 4 Robinetin IP, BDE, PDE, PA, and ETE energy values in kJ/mol

	Robinetin	Gas Phase	Benzene	DMSO	Methanol	Water
IP		454.00	594.79	452.58	450.82	439.11
BDE	3-OH	311.34	337.79	321.85	330.03	328.09
	3′-OH	340.43	317.97	316.97	321.26	324.44
	4′-OH	347.21	**282.31**	**282.69**	**291.06**	**294.25**
	5′-OH	**274.98**	345.69	332.21	330.26	344.21
	7-OH	347.99	352.73	349.29	364.47	366.87
PDE	3-OH	1185.10	154.73	− 12.18	67.11	78.35
	3′-OH	1214.19	134.91	− 17.06	58.35	74.70
	4′-OH	1220.96	99.25	− 51.34	28.15	44.50
	5′-OH	1148.73	162.63	− 1.82	67.35	94.47
	7-OH	1221.75	169.67	15.26	101.56	117.13
PA	3-OH	1102.01	430.17	125.28	149.51	186.41
	3′-OH	1121.34	382.75	93.83	169.66	167.06
	4′-OH	1082.66	348.23	66.94	129.57	147.71
	5′-OH	1126.64	436.10	127.16	172.37	191.69
	7-OH	1105.83	375.61	91.64	153.01	170.90
ETE	3-OH	537.08	319.35	315.13	368.42	331.04
	3′-OH	546.84	346.94	341.69	339.50	346.74
	4′-OH	592.30	345.81	334.29	349.40	335.90
	5′-OH	476.09	321.32	323.60	345.81	341.89
	7-OH	569.92	388.85	376.21	399.37	385.34

The values in bold typeface indicate the lowest value for a given solvent

major three radical-scavenging mechanisms: HAT, SET-PT, and SPLET. Therefore, the most active site for the radical-scavenging reaction and the thermodynamically preferable reaction pathway could be predicted. In addition to the gas phase, these parameters were computed in the presence of polar, non-polar, protic, and aprotic solvents. The solvents are organized from non-polar and aprotic to polar and protic starting from benzene, DMSO, methanol, then water.

The different positions of hydroxyls on A, B, and C rings of the flavonoid main structure directly impact on its radical scavenging potency. The most-active OH group of each studied flavonol was determined by the minimal sum of the enthalpies of the specific reaction pathways including BDE_{min}, $(IP+PDE)_{min}$, and $(PA+ETE)_{min}$ related to HAT, SET-PT, and SPLET mechanisms, respectively (based on the histograms in Fig. 5b and c and Fig. 6b and c). Robinetin exhibits a higher antioxidant activity than Fisetin and the 4′-OH hydroxyl was found as the preferred active site for both flavonols, independently of the solvent nature and the adopted mechanism.

Robinetin is more active than Fisetin as revealed by BDE (Tables 3 and 4); this is in agreement with the experimental published results for the reduction of DPPH radical (IC50: 11.02 ± 0.56 µM and 14.06 ± 0.21 µM) by Robinetin and Fisetin, respectively [77]. The most stable radical is 4′-O•, which results from a homolytic removal of the hydrogen atom from the OH group attached to the C4' position; it is mainly due to the hydrogen bond between 3-OH and the 4-oxo group and the keto-enol tautomerism via the 2,3-double bond and the benzyl cycle. For Fisetin, B-ring has the most active antioxidant hydroxyls then A-ring followed by C-ring: B-ring > C-ring > A-ring. It exhibits the following BDE, IP + PDE, and PA + ETE favorable hydroxyls 4′-OH > 3′-OH > 3-OH > 7-OH (Fig. 5a-c). For Robinetin, the most stable radical is also 4′-O• and exhibits the following BDE, IP + PDE, and PA + ETE order for the hydroxyl groups: 4′-OH > 3′-OH > 3-OH > 5′-OH > 7-OH (exceptionally 5′-ArO• in the gas phase) as depicted in Fig. 6a, b and c. Several studies of solvent effects on flavonoids showed that the most favorable hydroxyl associated with the antioxidant activity is 4′-OH as found in quercetin [78], myricetin [79], kaempferol [70], apigenin [80], and in diglycosylated flavonoids such isorhamnetin-3,5′-O-β-D-diglucoside and isorhamnetin-3,7-O-β-D-diglucoside [81].

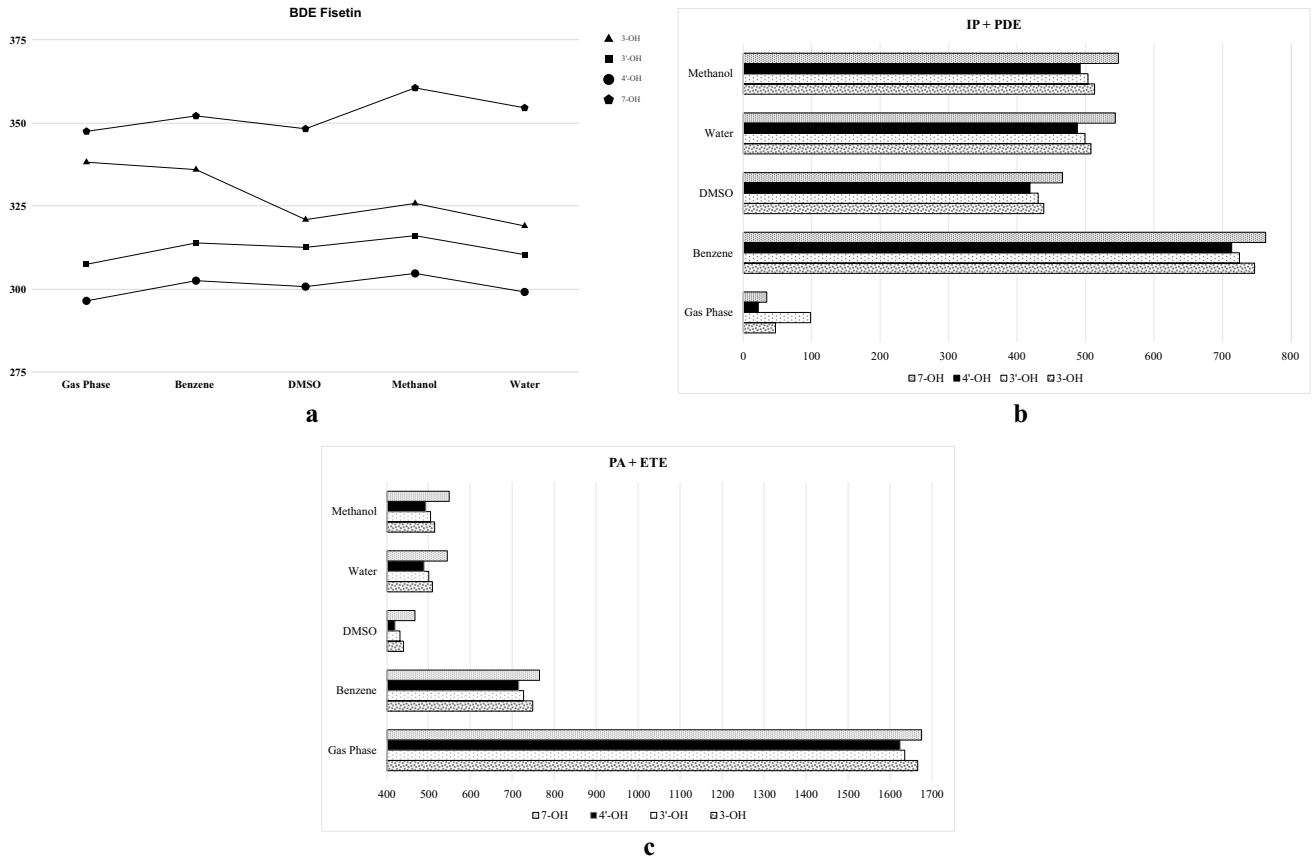

Fig. 5 Fisetin energy values in kJ/mol. **a** BDE. **b** IP + PDE. **c** PA + ETE

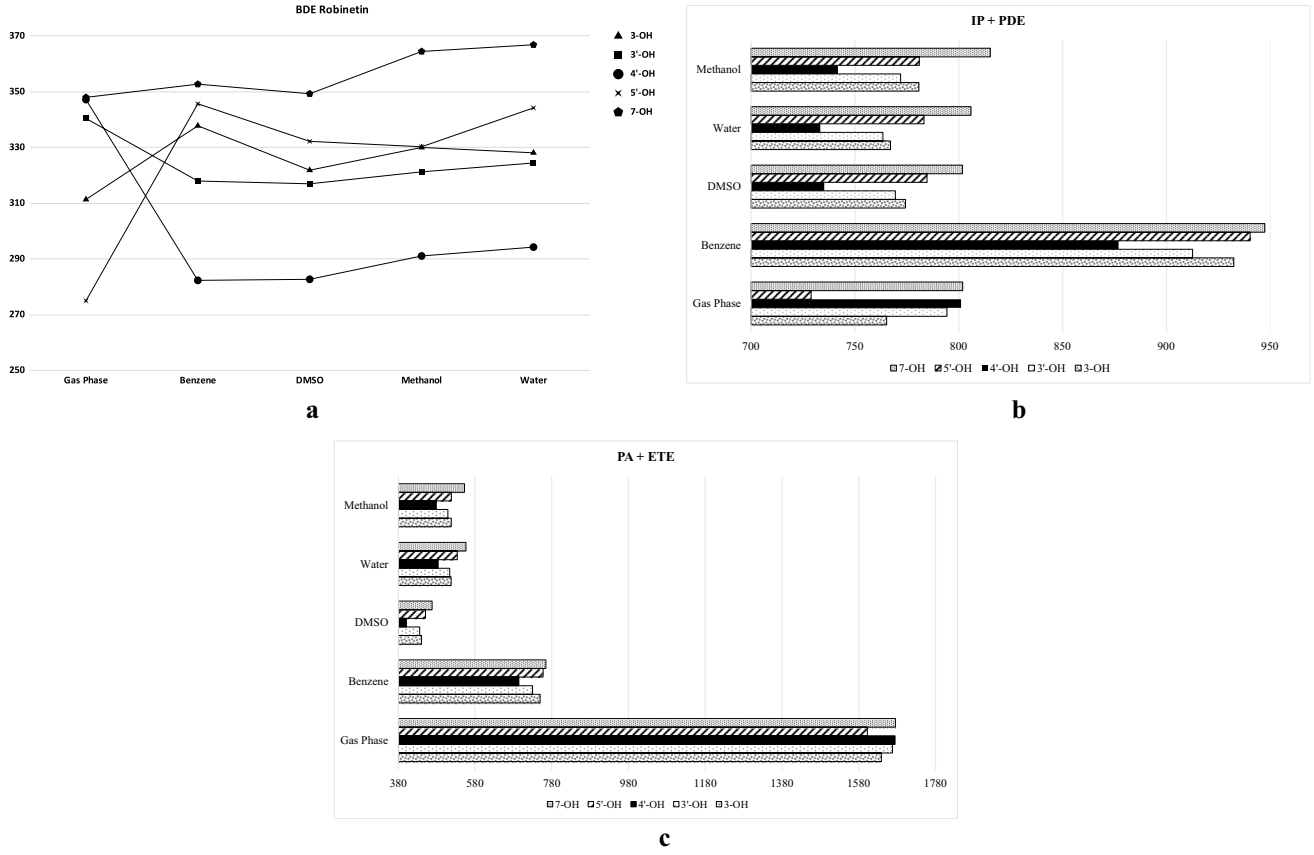

Fig. 6 Robinetin energy values in kJ/mol. **a** BDE. **b** IP + PDE. **c** PA + ETE

Compared to SET-PT and SPLET mechanisms, HAT is thermodynamically the most favored pathway [81] for the antioxidant activity of Fisetin and Robinetin (Tables 3 and 4). Fisetin 4′-O• radical has a BDE energy need of 296.46, 302.53, 300.73, 300.72, and 299.13 kJ/mol in gas phase, benzene, DMSO, methanol, and water, respectively. However, IP + PDE and PA + ETE values are higher than 400 kJ/mol as shown in Fig. 5b and c . Robinetin has BDE energy need of 347.21, 282.31, 282.69, 291.06, and 294.25 kJ/mol in gas phase, benzene, DMSO, methanol, and water

Table 5 4′-OH bond dissociation enthalpy values (kJ/mol) corresponding to the formation of radical species compared to reported values

4′-OH BDE	Gas phase	Benzene	DMSO	Methanol	Water	Theory level	Ref
Fisetin	355.72					B3LYP/6–31+G(d,p)	[43]
	302.67					B3LYP/6–311++G(d,p)	[39]
	308.91					B3LYP/6–311++G(d,p)	[82]
	289.67	299.71		301.38	292.60	B3LYP/6–31G(d,p)	[74]
	301.00	310.00			302.00	B3LYP/6–311++G(d,p)	[83]
	358.64					M06-2X/6–311+G(3df,2p)	[85]
	308.00					PM7	[47]
	293.94					PM6	[84]
	296.46	302.53	300.73	304.72	299.13	B3LYP/6–311++G(d,p)	This work
Robinetin	310.57					B3LYP/6-311G(d,p)	[49]
	315.30					wB97XD/cc-pvtz	[48]
	298.41					PM7	[47]
	347.21	282.31	282.69	291.06	294.25	B3LYP/6–311++G(d,p)	This work

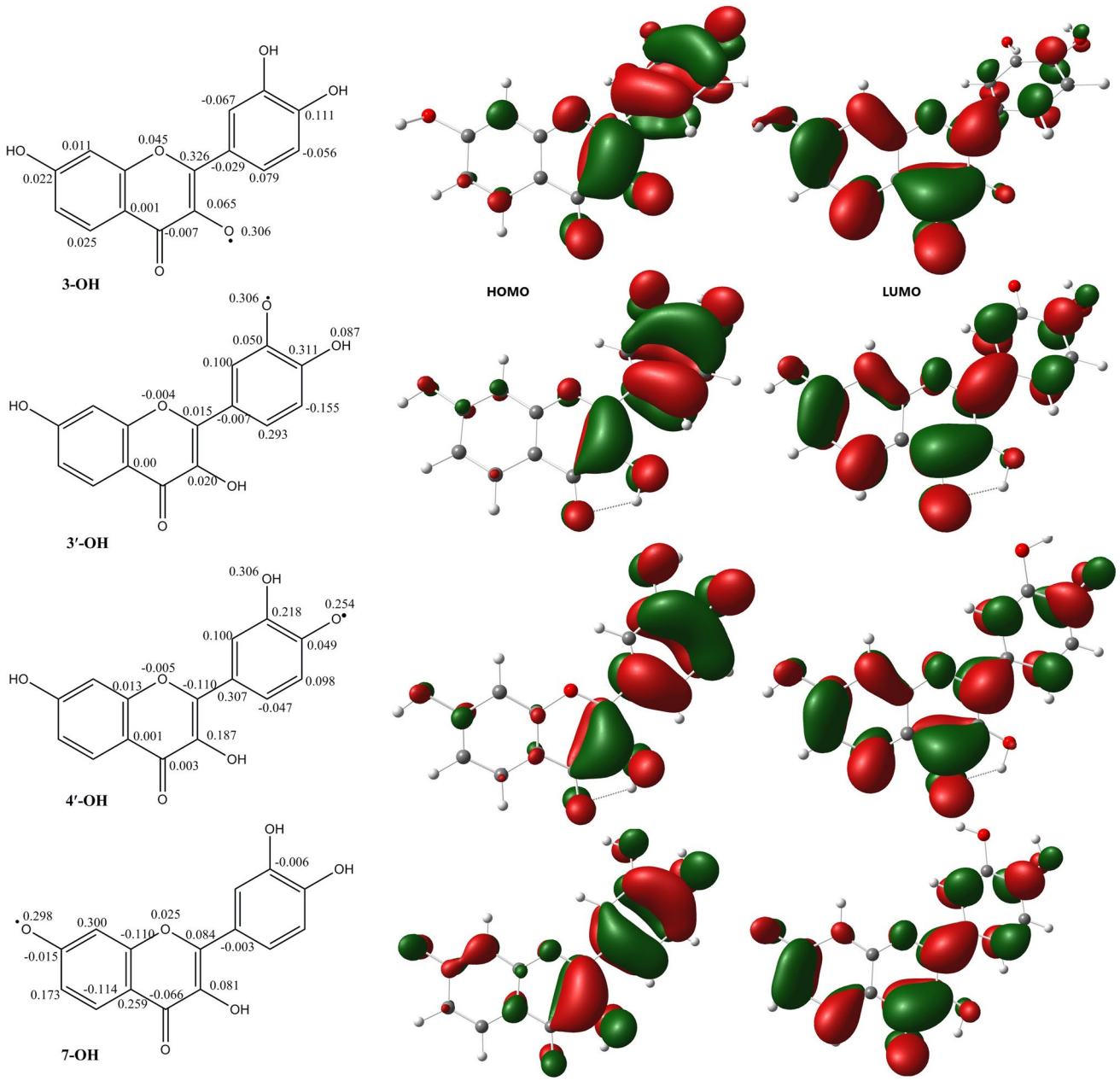

Fig. 7 HOMO, LUMO and spin densities of Fisetin radical species

respectively whereas IP + PDE and PA + ETE values are higher than 400 kJ/mol as shown in Fig. 6b and c.

Water is the most favored solvent (Fig. 5a); the BDE for 4′-O• Fisetin radical species pursues the following trend in solvents: water > DMSO > benzene > methanol; in contrast as shown in Fig. 6a, the favored solvent for 4′-O• Robinetin radical species is benzene: benzene > DMSO > methanol > water.

On the basis of the computed BDE, it has been demonstrated that the 4′-O• radical species is more stable than any other radical species. These results are in agreement with many previous BDE determined by various scientific reports [39, 47, 74, 82–84]. Through the analysis of the values shown in Table 5, it is possible to notice that the most BDE values were reported in gas phase; they vary in function of the level of theory: BDE values for Fisetin range from 289.67 [74] to 355.72 kJ/mol [43] calculated at B3LYP/6–31G(d,p) and B3LYP/6–31+G(d,p) levels of theory, respectively. Robinetin BDE values range from 298.41 [47] to 347.21 kJ/mol (this work) computed at PM7 and B3LYP/6–311++G(d,p), respectively.

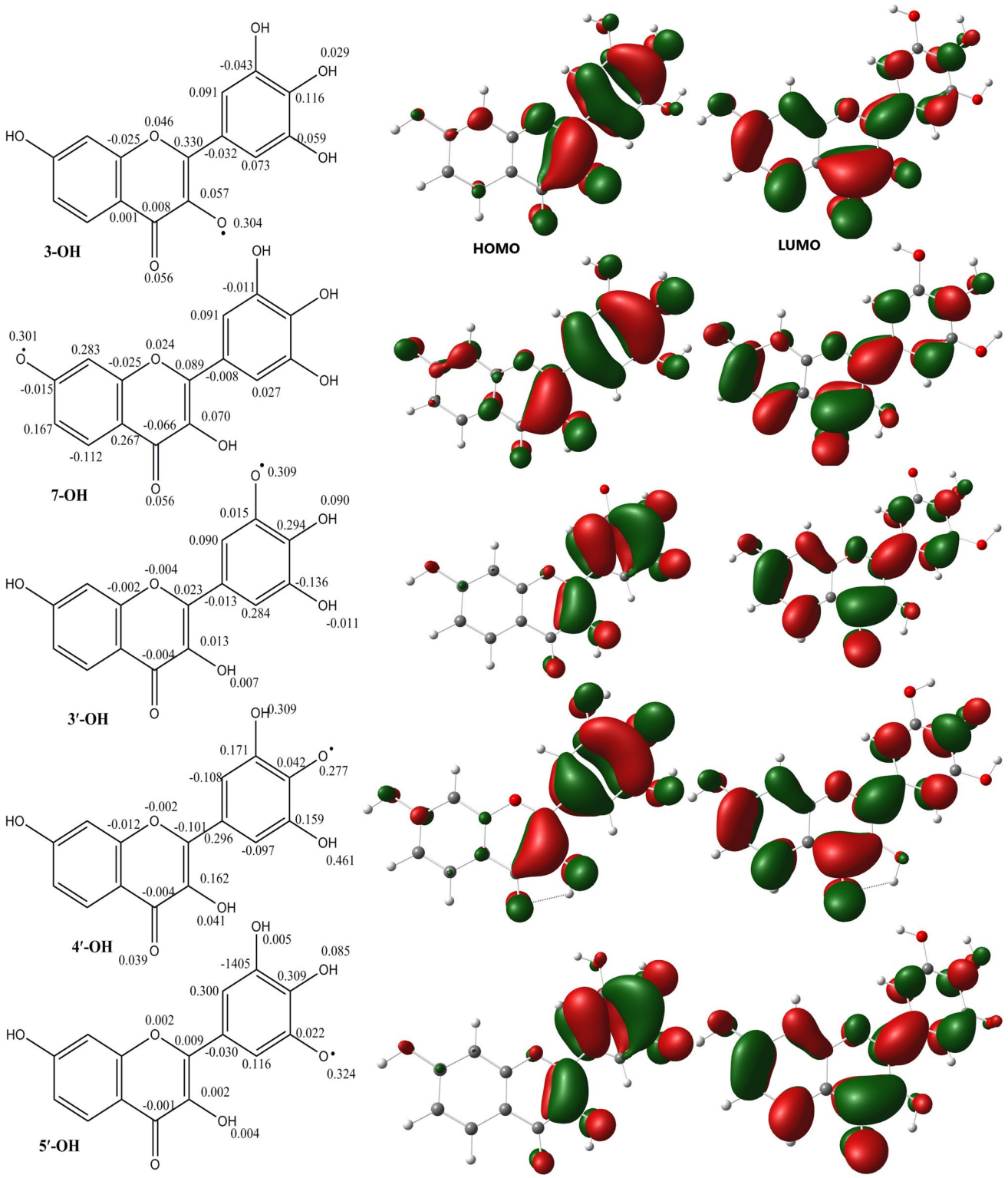

Fig. 8 Density plot of the HOMO and LUMO compositions of Robinetin radical species

HOMO, LUMO frontiers, spin densities, and the stability of the radical species

As shown in Fig. 7 and Fig. 8, the HOMO and LUMO frontier compositions of all the radical species related to both flavonols reveal clearly the presence of elevated charge density delocalization on the cinnamoyl part (C and B rings). Exceptionally, the 7-O• LUMO shows a charge density delocalization on the A-ring and slightly in C-ring which is probably due to the resonance in just one cycle A-cycle in contrary for the other radicals: 4′-O•, 3′-O•, 3-O•, 5′-O• where the resonance exists over the cinnamoyl part.

The spin densities are an important parameter which provides information about the stability of radicals. According to Parkinson [86], the more delocalized the spin density in the radical, the easier the radical formed, and thus the lower is the BDE. Spin densities for Fisetin and Robinetin species were calculated (Fig. 7 and 8).

On one hand, Fig. 7 shows the spin densities of the Fisetin radical species 3-O•, 3′-O• and 7-O• corresponding to 0.306, 0.306, and 0.298; these values are higher than the spin density of 4′-O• (0.254). On the other hand, Fig. 8 indicates that the spin densities of the Robinetin species 3-O•, 3′-O•, 5-O•, and 7-O• are 0.304, 0.309, 0.324, and 0.301 which are also higher than the spin density of 4′-O• (0.254). This means that the formation of 4′-O• is favorable, taking account that in this species, the spin densities are delocalized over the cinnamoyl part of the molecule, which contributes to the stability of the radical. Furthermore 4′-O• radical corresponds to the lowest BDE in all the studied solvents (Tables 3 and 4).

Conclusions

Quantum-chemical methods are still the reliable theoretical approaches to study flavonoids and their electronic properties, especially the antioxidant activity. In this work, density functional theory (DFT) method B3LYP/6–311++G(d,p) level of theory was utilized to investigate the antioxidant activity of two flavonols, namely, Fisetin and Robinetin, by comparing the following thermodynamic parameters: BDE, (IP + PDE), and (PA + ETE) related to the three fundamental mechanisms: Hydrogen-Atom Transfer (HAT), single Electron Transfer Followed by Proton Transfer (SET-PT), and sequential Proton Loss Electron Transfer (SPLET) mechanisms.

The results showed that 4′-OH hydroxyl is the preferred antioxidant active site for both Fisetin and Robinetin: 4′-OH > 3′-OH > 3-OH > (5′-OH) > 7-OH. Spin densities and orbital frontier analysis are in agreement with the stability of the 4′-O• radical species. HAT mechanism was found to be the most favored pathway besides the energetically preferred solvents, following the trends water > DMSO > benzene > methanol and benzene > DMSO > methanol > water for Fisetin and Robinetin, respectively.

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Rafik Menacer: writing—original draft, conceptualization, methodology, resources, data curation, software, investigation, formal analysis, visualization, validation, writing—review and editing. Rekkab Seifeddine: resources, data curation, software, investigation, visualization. Zahia Kabouche: supervision, validation, writing—review and editing.

Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors declare no competing interests.

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