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Theoretical Study of Radical Scavenging Antioxidant Activity of Coumarin Derivatives in Licorice Using DFT

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Abstract

Nowdays, much research is focused on exploring antioxidant activity based on natural compounds. Licorice, a traditional natural product rich in antioxidant components, has been widely used in clinical medicine. However, there is a lack of theoretical studies on the active components in licorice. In this context, the antioxidant activity of several common active components of coumarin derivatives in licorice was investigated using a density flooding theory (DFT) approach. The free radical scavenging ability of the compounds was achieved by hydrogen atom transfer (HAT), sequential electron transfer proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET) mechanisms. The effect of solvent on antioxidant activity was also investigated. It was found that in the gas and benzene phases, the compounds studied preferred to undergo the HAT mechanism, while SPLET was favoured in polar solvents. In addition to the above mechanism, the HOMO and LUMO energies of the compounds as well as molecular descriptors and electrostatic potential maps were calculated and applied to predict the antioxidant activity of the compounds. The above studies allow a better understanding of the mechanism of free radical scavenging activity of coumarin derivatives from licorice.

Keywords

Coumarin; Glycyrrhiza Glabra; Antioxidants; DFT; Free Radicals.

1. Introduction

Normal cellular metabolism is a continuous source of reactive oxygen species (ROS), which play pivotal roles in various biological functions. However, certain circumstances can lead to the conversion of oxygen into highly reactive forms, such as hydroperoxy radicals (HOO-), hydroxyl radicals (HO-), and nitrogen dioxide radicals (NO_2-), predominantly through chemical reactions within living organisms. While ROS at physiological levels participate in essential redox-dependent processes vital for physiological activities, excessive production of these molecules can overwhelm the body's defense mechanisms, potentially contributing to the onset of diverse pathologies including aging, cancer, inflammation, and cardiovascular diseases [1-4]. In such instances, supplementation with exogenous antioxidants becomes necessary to mitigate the overproduction of free radicals. Consequently, the development of efficacious antioxidants to rebalance ROS distribution holds therapeutic promise. Moreover, this endeavor holds significant clinical relevance for preserving cellular redox homeostasis and diminishing disease susceptibility [5-7].

Licorice, also known as Chinese Glycyrrhiza glabra (Gan Cao), encompasses a spectrum of bioactive constituents including flavonoids, triterpenoid saponins, coumarins, and phenols, among others. Originating from the roots and rhizomes of Uralic Glycyrrhiza glabra, this traditional Chinese medicine boasts a rich historical background [8]. Widely employed across numerous countries, licorice finds utility in treating various ailments such as viral infections, respiratory disorders, and rheumatism [9-11].Among its constituent compounds, coumarin emerges as a significant natural organic product renowned for its potential antioxidant properties. Coumarins extracted from Glycyrrhiza glabra present diverse structural configurations, including Glycyrin (GLYr), Glycycoumarin (GLYc), 7,2',4'-Trihydroxy-5-Methoxy-3-phenylcoumarin (COA), and Inflacoumarin A (INA), among others [12,13], as depicted in Figure 1. Notably, their pharmacological activities have been progressively elucidated through experimental studies. For instance, GLYr has demonstrated noteworthy anti-hepatitis C virus (HCV) activity, exhibiting an IC50 value of 7.2 μg/mL, indicating its potential as a promising candidate for anti-HCV drug development [14].Furthermore, Kuroda et al. elucidated GLYr's role as a primary ligand for the peroxisome proliferator-activated receptor, PPAR-γ, showcasing its ability to effectively reduce blood glucose levels in genetically diabetic mice [15]. The isoprene moiety at C-6 within the arylcoumarin backbone and the C-2′ hydroxyl group in the aryl ring portion were identified as pivotal sites for PPAR-γ ligand binding activity. Additionally, licorice coumarins such as GLYr and GLYc, representative compounds, exhibited potent ABTS and DPPH radical scavenging capabilities, indicative of their antioxidant potential [16,17]. COA, on the other hand, demonstrated inhibitory activity against prostate-specific antigens secreted by androgen-dependent prostate cancer cell lines [18].

Despite previous endeavors, the pharmacological activities of licorice coumarins, particularly their antioxidant effects and underlying mechanisms, remain inadequately comprehended and even contentious in certain aspects [19]. Consequently, there exists a necessity to delve deeper into the antioxidant potency and plausible mechanisms of licorice coumarins to steer the development of novel antioxidants and drug precursors predicated on this significant chemical scaffold. The exploration of natural product antioxidant properties via density functional theory (DFT) has emerged as a potent investigative tool over the past few decades [20]. Functioning as a theoretical research methodology, DFT has proven efficacious in elucidating several mechanisms.Adam Mechler's team employed the DFT approach to scrutinize the role of the benzyl hydrogen atom within the lignin family concerning antioxidant properties. Their findings underscored the pivotal nature of the benzyl C-H bond in the hydrogen atom transfer (HAT) process [21]. Subsequently, Alisi et al. rationalized the design of potent antioxidant derivatives of curcumin through a ligand-based virtual screening approach utilizing the DFT method and assessed their free radical scavenging mechanisms via thermodynamic studies [22]. Moreover, Yang et al. investigated the antioxidant activity and mechanism of erucic acid and ferulic acid, with DFT calculations revealing a consistent alignment between the theoretical order of antioxidant activity and the results obtained from DPPH and FRAP experiments [23].More recently, Chen and collaborators employed DFT to compute the free radical trapping potency and mechanism of coumarin coumestan and its derivatives, elucidating the pivotal role of the o-dihydroxyl group in its D ring in free radical trapping [24]. These theoretical calculations have significantly enriched the comprehension of natural product antioxidant activities and mechanisms, offering invaluable insights for the design and refinement of natural products into more potent antioxidants.

In this study, we propose to investigate the antiradical properties of the aforementioned licorice coumarin constituents from a theoretical standpoint. It is well-established that the antiradical activity of phenolic compounds primarily stems from the presence of aromatic OH groups. Furthermore, numerous studies have highlighted the significance of certain CH bonds in dictating the antiradical properties of various natural products [25,26]. Therefore, we conducted an in-depth examination of all potential CH and OH bonds within the considered compounds, coupled with comparative analyses.To the best of our knowledge, there are no existing comparative density-functional theory (DFT) studies elucidating the antiradical properties of the selected compounds (Figure 1). Employing DFT calculations at the B3LYP-D4/def2-TZVP level of theory, we computed several structural features, including molecular descriptors such as electronegativity, softness, hardness, and electrophilic index. Additionally, we investigated the front molecular orbitals (HOMO and LUMO) and conducted molecular electrostatic potential (MEP) mappings.Moreover, we delved into the thermodynamic descriptors of the three primary antiradical mechanisms: hydrogen atom transfer (HAT), sequential electron transfer proton transfer (SETPT), and sequential proton loss electron transfer (SPLET). Through this comprehensive approach, we aim to provide valuable insights into the antiradical properties of licorice coumarin constituents, shedding light on their potential applications and mechanisms of action.

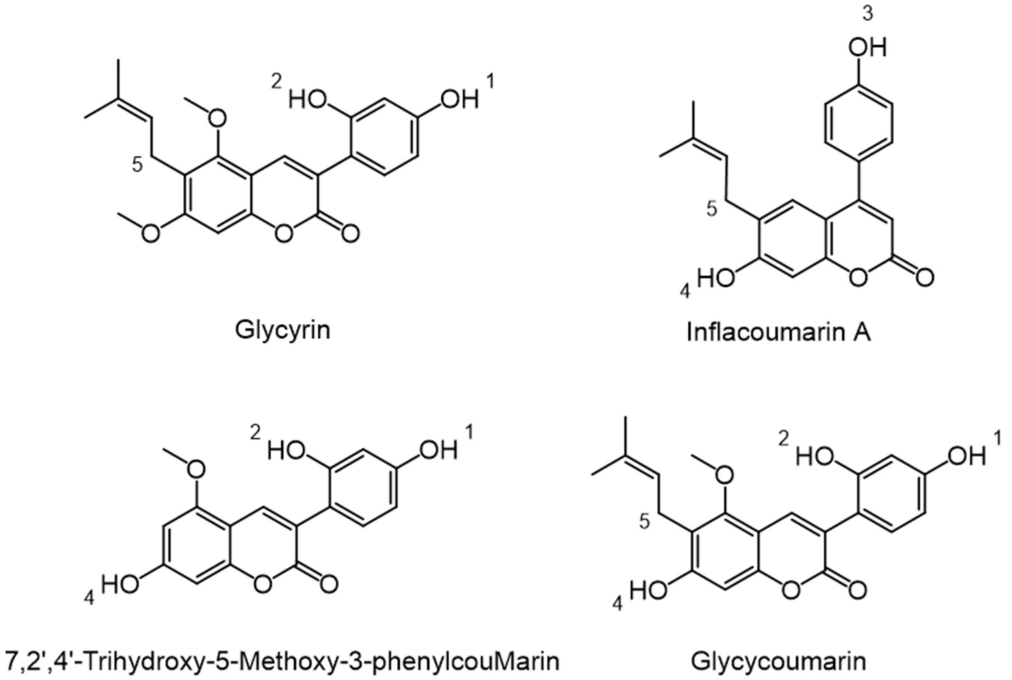

Figure 1. Molecular structures and atomic numbering of the studied licorice coumarins.

2. Calculation Method

The calculations described in this paper were conducted utilizing the ORCA5 program package [27]. Geometry optimization and frequency analysis of all studied species, including radicals, radical cations, and anions, were carried out at the DFT level using the B3LYP generalized functional and Def2-SVP basis set for all calculations. To refine the energies, single-point energy calculations were performed on the optimized structures at the B3LYP/Def2-TZVP level.The reliability of the DFT/B3LYP approach in computing thermodynamic parameters related to antioxidant activity has been corroborated by previous investigations on aromatic compounds. Solvent effects were accounted for using the polarized continuum medium model (SMD) with dielectric constants (ε) of 2.27, 24.85, and 78.35 to emulate benzene, ethanol, and water solvent effects, respectively. All ground states were validated through vibrational frequency analysis, ensuring absence of imaginary frequencies.Electronegativity, chemical softness, chemical hardness, and electrophilic index were computed based on HOMO and LUMO energies as reported in the literature. Molecular descriptors were calculated utilizing the Multiwfn package [28] and visualized using VMD [29].The thermodynamic descriptors for the antiradical mechanisms, namely bond dissociation enthalpy (BDE), ionization potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA), and electron transfer enthalpy (ETE), were determined using the following equations [24,30].

$$\mathrm{BDE} = \mathrm{H}\left(\mathrm{R}^{*}\right) + \mathrm{H}\left(\mathrm{H}^{*}\right) - \mathrm{H}(\mathrm{RH}) \tag{1}$$

$$\mathrm{IP} = \mathrm{H}\left(\mathrm{RH}^{*+}\right) + \mathrm{H}(\mathrm{e}^{-}) - \mathrm{H}(\mathrm{RH}) \tag{2}$$

$$\mathrm{PDE} = \mathrm{H}\left(\mathrm{RO}^{*}\right) + \mathrm{H}(\mathrm{H}^{+}) - \mathrm{H}\left(\mathrm{RH}^{*+}\right) \tag{3}$$

$$\mathrm{PA} = \mathrm{H}(\mathrm{R}^{-}) + \mathrm{H}(\mathrm{H}^{+}) - \mathrm{H}(\mathrm{RH}) \tag{4}$$

$$\mathrm{ETE} = \mathrm{H}\left(\mathrm{R}^{*}\right) + \mathrm{H}(\mathrm{e}^{-}) - \mathrm{H}(\mathrm{R}^{-}) \tag{5}$$

Enthalpies were obtained by thermally correcting the electron energies by adding zero-point energy (ZPE), translational, rotational, and vibrational contributions. All enthalpies were calculated for 298.15 K and 1.0 atmospheres (101.325 kPa).The enthalpies in the H (H^*), H (H^+) and H (e^-) gas phases and solvents were obtained from the literature [31]. Calculated enthalpies were performed using the Shermo program [32].

3. Results and Analysis

3.1. Geometric Structural Features and Molecular Descriptors

The molecular structures of the studied compounds GLYr, GLYc, COA and INA have been optimized by DFT calculations using B3LYP/Def2-SVP level of theory. The optimized molecular geometries are shown in Figure 2. It can be seen that only GLYr, GLYc and COA form hydrogen bonds between the phenolic hydroxyl group and the carbonyl group at distances of 1.63, 1.64 and 1.64 Å in the gas phase, respectively.

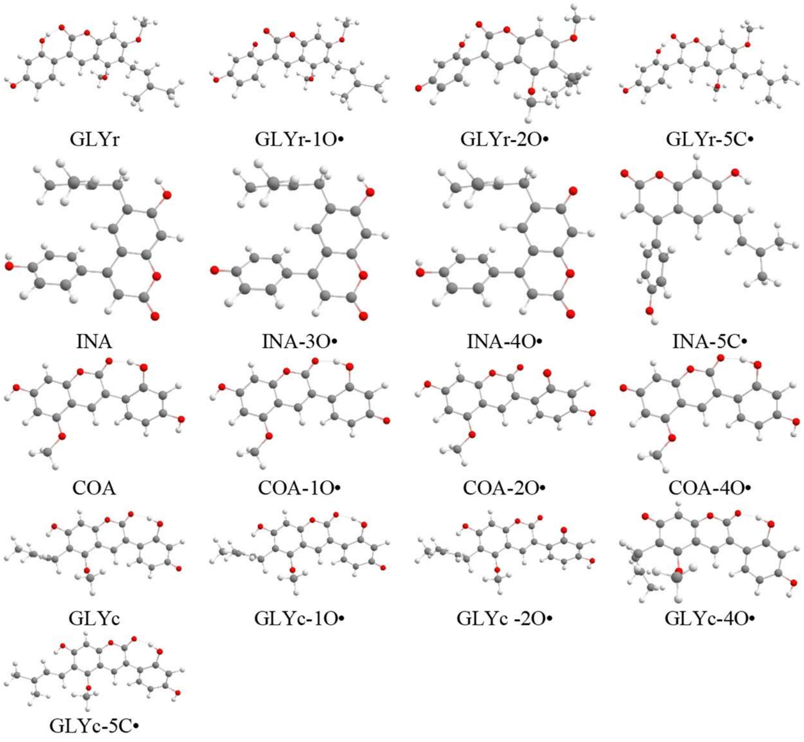
GLYr GLYr-1O• GLYr-2O• GLYr-5C•
INA INA-3O• INA-4O• INA-5C•
COA COA-1O• COA-2O• COA-4O•
GLYc GLYc-1O• GLYc -2O• GLYc-4O•
GLYc-5C•

Figure 2. The geometry of GLYr, GLYc, COA and INA and their radical forms in the gas phase.

The antiradical properties of the studied compounds can be estimated by calculating some molecular descriptors such as electronegativity, softness, hardness and electrophilic index [33,34]. Electronegativity is a measure of the tendency to attract electrons in a chemical bond. Chemical softness and hardness are measures of charge transfer resistance. The electrophilic index is related to the energy reduction associated with the maximum electron flow between the donor and acceptor. All these descriptors obtained from the HOMO/LUMO energy method were calculated at the B3LYP/Def2-TZVP level of theory and the values obtained are described in Table 1.

Table 1. Molecular descriptors in eV of GLYr, GLYc, COA and INA obtained at B3LYP/Def2-TZVP level of theory

Molecular descriptors	GLYr	GLYc	COA
Electronegativity	3.9673	4.0293	3.9455
Softness	0.1605	0.1586	0.1561
Hardness	6.2315	6.3065	6.4069
Electrophilic index	1.2629	1.2872	1.2148

As shown in Table 1, the electronegativity, softness, hardness and electrophilic index of all the studied compounds were relatively comparable with 3.9455-4.0293, 0.1561-0.1605, 6.2315-6.4069 and 1.2148-1.2872, respectively, except for INA. These results indicate that these compounds preferred to act as electron donors rather than electron acceptors in the studied media than as electron acceptors. For INA, the electronegativity (4.0856) and electrophilic index (1.1673) were higher than the other compounds. This indicates that INA is the worst electron donor compound among the studied compounds and hence a less reactive antiradical agent.

3.2. Frontline Molecular Orbitals and MEP

The lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital, HOMO, are important parameters for characterizing the antiradical activity of organic compounds.The energy of the HOMO correlates with the ability to provide electrons, while the shape of the HOMO determines the site of radical attack. Molecules with lower HOMO energies are less likely to provide electrons [35]. The calculated LUMO and HOMO energies and distributions of GLYr, GLYc, COA, and INA in the gas phase are shown in Table 1.GLYr presents a higher HOMO energy (-5.63 eV) in the studied compounds, which indicates that this compound has the strongest ability to provide electrons.INA has a lower HOMO energy (-6.14 eV), which indicates that this compound is the weakest electron donor and therefore the least effective antiradical agent. Based on the HOMO energies, the electron donating ability of the studied compounds is GLYr > COA > GLYc > INA.These results are in good agreement with the calculated ionization potential (IP) values (discussed in the next section). Furthermore, it can be seen that the HOMO and LUMO of all the studied compounds are located around the non-isoprene substituents. This suggests that isoprene substituents may play a minor role in the overall reactivity of these molecules.

MEP mapping is to analyze and predict molecular reactivity [36,37]. The results of MEP mapping for GLYr, GLYc, COA and INA calculated at the B3LYP/Def2-TZVP level of theory are shown in Figure 1. Nucleophilic and electrophilic sites are indicated by different color codes; dark blue indicates electron-rich sites, while dark red indicates electron-deficient sites. As can be seen from Figure 3, the most electron-rich sites for all studied phenolic compounds (GLYr, GLYc, and INA) are located around the oxygen atom of the phenolic hydroxyl group, while the most electron-deficient sites are located around the isoprene substituent. For COA, the most electron-rich site is located around the oxygen atom of the phenolic hydroxyl group, but the most electron-deficient site is located near the methoxy group. These results can be used to predict the sites of free radical attack, but antiradical action is a complex and diverse process that may be influenced by several factors [38,39]. In order to better understand the antiradical properties of the studied compounds, thermodynamic parameters related to the main antiradical mechanisms were investigated and the results obtained are examined in the next section.

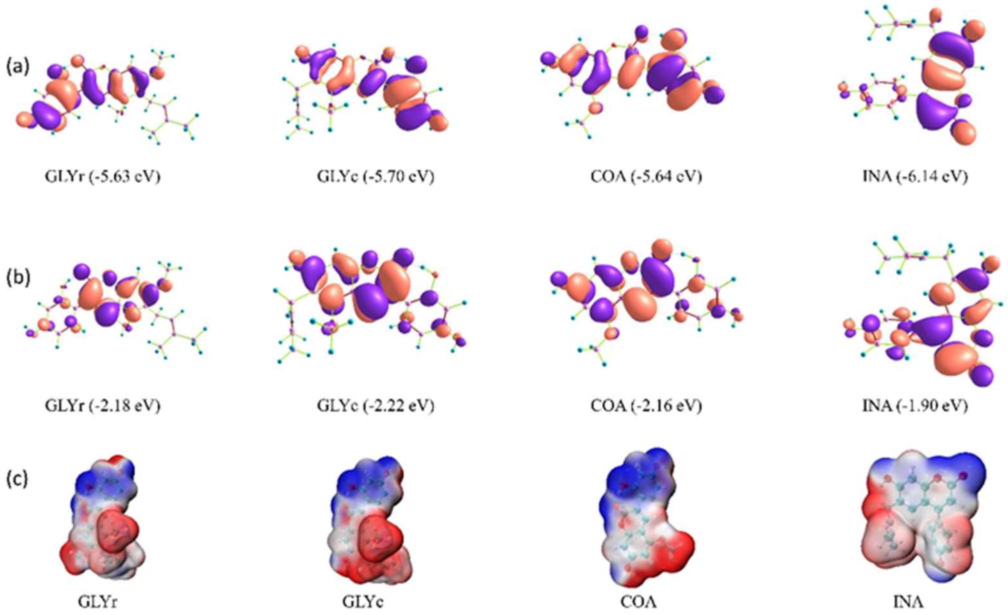

Figure 3. Highest occupied molecular orbital (a), lowest unoccupied molecular orbital (b), and molecular electrostatic potential (c) of the studied compounds calculated at B3LYP/Def2-TZVP level of theory.

4. Mechanistic Study

4.1. HAT Mechanism

Calculated BDE values for all possible benzyl C-H and hydroxy O-H of the studied licorice coumarins GLYr, GLYc, COA and INA in the gas and solvent phases are given in Table 2. As mentioned earlier, the results obtained for these four compounds showed that the benzyl C-H group had the lowest BDE values. For the OH group, the lowest value was determined for the 4-OH group, but it was not much different from 1-OH. This agrees well with the results of the frontline molecular orbitals and the molecular electrostatic potentials.The BDE value for 2-OH is the largest in all groups (GLYr, GLYc and COA), which can be attributed to the hydrogen in 2-OH forming a hydrogen bond with the adjoining C=O. This hydrogen bonding effect was also confirmed in a previous report [40]. In the gas phase, the. Comparison between COA and GLYc reveals that the introduction of isoprene substituents reduces the BDE values of other OH bonds and improves their reactivity. The antioxidant effect of some coumarins has been reported to promote the release of hydrogen as a free radical via the benzyl hydrogen atom [25], which is consistent with the above results. The obtained data also showed that the effect of solvent (benzene, ethanol and water) on the BDE values of OH bonds was minimal for all the compounds studied, which is in agreement with previous studies. However, there is a very strong effect on the benzylic hydrogen of the isoprene substituent, which is reflected in the fact that the solvent inhibits the breakage of the CH and this effect is more pronounced the lower the polarity of the solvent, which is in agreement with previous studies [21,41]. Based on the calculated BDEs, the ability of the studied compounds to supply hydrogen via the HAT mechanism can be carried out on the order of GLYc = INA > GLYr > COA.

Table 2. Calculated BDE values of the studied coumarins and the reference compound Trolox in the gas phase and solvents

Comp.	BDE		
	Gas	Benzene	Ethanol
GLYr			
1	83.25	83.55	82.58
2	88.57	88.50	84.06
5	74.61	76.03	75.85
INA			
3	83.64	84.91	85.57
4	81.06	82.61	83.59
5	73.87	75.19	74.93
COA			
1	82.40	83.07	82.34
2	89.38	89.09	84.58
4	79.44	81.22	82.29
GLYc			
1	79.77	83.17	82.96
2	86.98	89.28	84.10
4	78.75	83.12	81.25
5	73.49	77.98	76.47
Trolox[a]	73.0	73.9	72.6

[a] The Trolox values are included for comparison, see Wang et al[42].

4.2. SETPT Mechanism

Unlike the HAT mechanism, the SETPT mechanism proceeds in two steps. The first is the transfer of electrons to radicals and the formation of cationic radicals, and the second is the deprotonation of the formed cationic radicals [43]. These steps are estimated by two thermodynamic indices, namely IP and PDE.The IP and PDE values of GLYr, GLYc, COA, and INA for all potential hydrogen atoms in different media (gas phase, benzene, ethanol, and water) were calculated as shown in Table 3.From this it can be seen that the lowest IP values in the gas phase were obtained with GLYc (157.03 kcal/mol) and GLYr (159.31 kcal/mol) were obtained. These compounds have relatively comparable electron supply capacity. Whereas, INA has a relatively high IP (174.17 kcal/mol) compared to the studied compounds. In contrast, IP obeys GLYr = GLYc = COA > INA in the gas phase, while a similar trend was found in each solvent GLYr = GLYc = COA. These results indicate that GLYr, GLYc, and COA have the same ability to donate electrons in all four media, while INA is the least effective. Unlike the case of BDE, in solution, the IP values of all the compounds studied were significantly lower than those in the gas phase, and the greater the polarity of the solvent, the greater the decreasing value, which can be attributed to the stabilization of the charged system experienced in polar solvents due to the high solvation enthalpy of the electrons.The decreasing order of the IP values was gas phase>benzene>ethanol>water, a finding that is similar to that of the other phenolic compounds reported[44] . These results reveal the importance of solvent polarity in controlling the SETPT mechanism of licorice coumarin.

As mentioned above, PDE is the enthalpy of deprotonation of cationic radicals.The PDE value indicates the thermodynamically preferred hydrogen atom for deprotonation. As shown in the table, INA has the lowest PDE (215.55 kcal/mol) as compared to the compounds studied. 1-OH and 2-OH have the highest BDE in each medium, while 5-CH benzyl hydrogen has the lowest BDE value. Thus 5-CH benzyl hydrogen seems to be the most active in the deprotonation step. In the solvents studied, all PDE values were significantly lower in the order of gas phase > benzene > ethanol > water. This confirms that polar solvents can promote deprotonation. These results are also in agreement with previous studies [45].

Assuming the SETPT mechanism, the antiradical activity was defined by the combination of PDE and IP values.The lower the IP + PDE value, the higher the antiradical activity. Based on the calculated IP + PDE values, the antiradical activities of the compounds studied by the SETPT mechanism can be carried out in the order GLYr ≈ INA ≈ GLYc > COA. This order is similar to the order obtained using the HAT mechanism. As shown, the IP (e.g., gas phase 157.03-160.97 kcal/mol) of the selected study compounds (GLYr, GLYc, and COA) is comparable to that of Trolox (e.g., gas phase 159.1 kcal/mol), suggesting that the electron-donating capacity of the studied glycyrrhizic coumarins is comparable to that of Trolox.

Table 3. Calculated IP and PDE values for the studied coumarins in the gas phase and solvents

Comp.	IP				PDE			
	Gas	Benzene	Ethanol	Water	Gas	Benzene	Ethanol	Water
GLYr	159.31	138.28	107.69	100.31				
1					239.78	44.23	21.93	27.10
2					245.10	49.19	23.41	28.58
5					231.14	36.72	15.20	21.00
INA	174.17	150.42	118.05	110.47				
3					225.32	33.45	14.56	20.15
4					222.73	31.16	12.58	18.59
5					215.55	23.74	3.91	10.08
COA	160.97	138.72	107.13	99.70				
1					237.27	43.32	22.24	27.53
2					244.25	49.34	24.48	29.71
4					234.31	41.47	22.19	27.72
GLYc	157.03	138.84	107.53	99.93				
1					238.58	43.30	22.46	27.60
2					245.80	49.41	23.60	28.82
4					237.57	43.25	20.75	27.17
5					232.31	38.10	15.97	21.99
Trolox[a]	159.1	136.8	105.9	98.0	229.8	37.0	13.8	21.2

[a] The Trolox values are included for comparison, see Wang et al[42].

4.3. SPLET Mechanism

The calculated PA and ETE values of GLYr, GLYc, COA and INA for all potential hydrogen atoms in gas phase, benzene, ethanol and water are shown in Table 4. Examination of the obtained results showed that in the gas phase, all the studied compounds had high PAs ranging from 318.63 to 353.54 kcal/mol. in benzene, ethanol and water solvents, all the PAs were significantly reduced by about 100 and 50 kcal/mol, respectively, suggesting that deprotonation in the solvent phase is much easier than that in the gas phase and implying that polar solvents are favorable for deprotonation of the examined systems. The ETE values characterize the second step of the SPLET mechanism [46], as shown in Table 4, the ETE values of all the studied compounds in the gas phase were relatively small, ranging from 13.52 to 70.56 kcal/mol. in solution (benzene, ethanol and water), the results obtained indicated that the solvents led to a significant increase in the ETE of all the studied compounds. It was also found that the ETEs in the studied media were much lower than the corresponding IPs, suggesting that the anionic form of the electron donor is preferable to the neutral form for all the compounds studied. Similar results were found in previous studies [47,48]. Thermodynamically, the energy required for the SPLET mechanism is equal to the energy required for the SETPT mechanism because the end products are the same free radicals in both mechanisms. Therefore, the trend of antiradical activity of the SPLET mechanism for the studied compounds must be GLYr = GLYc = COA > INA.

Table 4. Calculated PA and ETE of the studied coumarins in the gas phase and solvents

Comp.	PA				ETE			
	Gas	Benzene	Ethanol	Water	Gas	Benzene	Ethanol	Water
GLYr								
1	338.09	103.48	44.60	47.02	61.00	79.04	85.02	80.39
2	345.34	108.79	45.38	47.14	59.07	78.69	85.72	81.76
5	353.54	122.70	72.88	76.92	36.92	52.30	50.01	44.39
INA								
3	329.60	97.32	42.94	45.53	69.88	86.56	89.67	85.10
4	326.22	93.47	39.05	42.03	70.68	88.11	91.58	87.03
5	350.59	119.37	69.89	74.26	39.12	54.79	52.07	46.29
COA								
1	339.08	103.77	45.16	47.26	59.16	78.27	84.21	79.97
2	347.46	109.84	46.22	47.96	57.76	78.23	85.39	81.45
4	321.04	89.74	38.18	41.11	74.25	90.45	91.15	86.31
GLYc								
1	335.37	103.17	44.63	46.85	60.24	78.98	85.36	80.67
2	343.89	109.29	45.09	46.65	58.93	78.96	86.04	82.10
4	318.63	90.95	37.06	40.23	75.96	91.14	91.22	86.87
5	346.03	120.10	71.65	75.89	43.30	56.84	51.86	46.04
Trolox[a]	347.1	109.4	52.0	56.8	41.9	64.4	67.8	62.4

a The Trolox values are included for comparison, see Wang et al[42].

5. Evaluation of Thermodynamically Preferred Mechanisms

It is well known that the preferred mechanism of antiradical activity can be determined by comparing the BDE, IP and PA values, where IP and PA are related to the first step of the SETPT and SPLET mechanisms, respectively. As can be seen in Figure 4, IP and PA are significantly higher than the corresponding BDE values in the gas and benzene phases. For example, the lowest BDE for GLYr in the gas phase is about 85 and 263 kcal/mol lower than the corresponding IP and PA values, respectively.This suggests that HAT is the main mechanism for all studied compounds in these media. These results are in good agreement with previous studies on phenolic compounds. In the polar solvents ethanol and water, the large reduction in PA observed allowed SPLET to compete with HAT. In the case of GLYr, GLYc, COA, and INA, their PAs were significantly lower than those of BDE and IPs. for example, the PA of GLYc was approximately 40 kcal/mol lower than that of BDE in ethanol solvent. this makes SPLET the primary mechanism in the polar solvent ethanol and water, which is also in agreement with previous studies [49]. Interestingly, for GLYr, GLYc, COA, and INA, PA was comparable to BDE, suggesting that both HAT and SPLET favor these compounds in the solvents (benzene, ethanol, and water). The IP values of the studied compounds are significantly higher than the other thermodynamic descriptors in all the studied media, indicating that the SETPT mechanism is the least favored mechanism in the studied media.

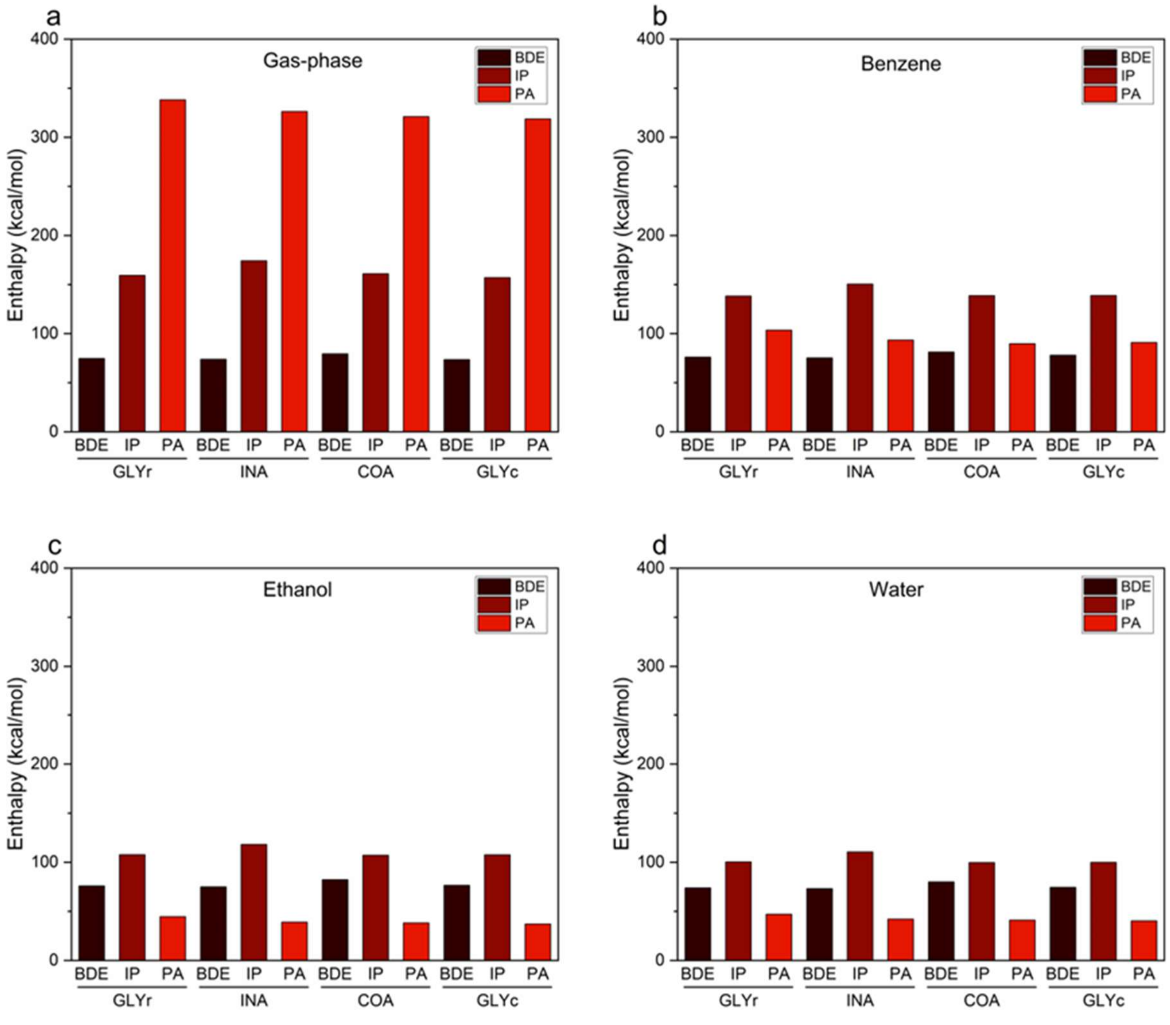

Figure 4. Calculated BDE, IP, and PA values for the studied compounds in gas-phase, benzene, ethanol and water.

6. Conclusion

In this study, the free radical scavenging properties of several licorice coumarins were evaluated by DFT calculations. Several thermodynamic descriptors (BDE, IP, PDE, PA, and ETE) associated with antiradical effects were calculated. The main mechanisms such as HAT, SET-PT and SPLET were discussed in detail. It was determined that in the gas and benzene phases, the studied compounds are more inclined to undergo the HAT mechanism, while SPLET is the main mechanism in polar solvents (ethanol and water). The above study allows a better understanding of the mechanism of free radical scavenging activity of coumarin derivatives from licorice. Overall, the present study contributes to a deeper understanding of the antioxidant activity and mechanism of licorice coumarins, and provides useful guidelines for improving the antioxidant capacity of licorice coumarins and designing them as drug candidates or nutraceuticals.

References

[1] X.Q. Wang, W. Wang, M. Peng, X.Z. Zhang, Free radicals for cancer theranostics, in: Secondary X.Q. Wang, W. Wang, M. Peng, X.Z. Zhang (Eds.) Secondary Free radicals for cancer theranostics, Publisher, Place Published,Vol.266 (2021), p. 120474.

[2] K.J. Romero, M.S. Galliher, D.A. Pratt, C.R.J. Stephenson, Radicals in natural product synthesis, in: Secondary K.J. Romero, M.S. Galliher, D.A. Pratt, C.R.J. Stephenson (Eds.) Secondary Radicals in natural product synthesis, Publisher, Place Published,Vol.47 (2018), p. 7851-7866.

[3] S. Di Meo, P. Venditti, Evolution of the Knowledge of Free Radicals and Other Oxidants, in: Secondary S. Di Meo, P. Venditti (Eds.) Secondary Evolution of the Knowledge of Free Radicals and Other Oxidants, Publisher, Place Published,Vol.2020 (2020), p. 9829176.

[4] V. Fasiku Oluwaseun, C.A. Omolo, T. Govender, Free radical-releasing systems for targeting biofilms, in: Secondary V. Fasiku Oluwaseun, C.A. Omolo, T. Govender (Eds.) Secondary Free radical-releasing systems for targeting biofilms, Publisher, Place Published,Vol.322 (2020), p. 248-273.

[5] K. Neha, M.R. Haider, A. Pathak, M.S. Yar, Medicinal prospects of antioxidants: A review, in: Secondary K. Neha, M.R. Haider, A. Pathak, M.S. Yar (Eds.) Secondary Medicinal prospects of antioxidants: A review, Publisher, Place Published,Vol.178 (2019), p. 687-704.

[6] V.D. Kancheva, A.K. Slavova-Kazakova, S.E. Angelova, S.K. Singh, S. Malhotra, B.K. Singh, L. Saso, A.K. Prasad, V.S. Parmar, Protective effects of 4-methylcoumarins and related compounds as radical scavengers and chain-breaking antioxidants, in: Secondary V.D. Kancheva, A.K. Slavova-Kazakova, S.E. Angelova, S.K. Singh, S. Malhotra, B.K. Singh, L. Saso, A.K. Prasad, V.S. Parmar (Eds.) Secondary Protective effects of 4-methylcoumarins and related compounds as radical scavengers and chain-breaking antioxidants, Publisher, Place Published,Vol.140 (2017), p. 133-145.

[7] B. Halliwell, Free radicals and antioxidants - quo vadis?, in: Secondary B. Halliwell (Ed.) Secondary Free radicals and antioxidants - quo vadis?, Publisher, Place Published,Vol.32 (2011), p. 125-130.

[8] X. Li, R. Sun, R. Liu, Natural products in licorice for the therapy of liver diseases: Progress and future opportunities, in: Secondary X. Li, R. Sun, R. Liu (Eds.) Secondary Natural products in licorice for the therapy of liver diseases: Progress and future opportunities, Publisher, Place Published,Vol.144 (2019), p. 210-226.

[9] Q. Wang, X. Qiao, Y. Qian, C.F. Liu, Y.F. Yang, S. Ji, J. Li, D.A. Guo, M. Ye, Metabolites identification of glycyrin and glycyrol, bioactive coumarins from licorice, in: Secondary Q. Wang, X. Qiao, Y. Qian, C.F. Liu, Y.F. Yang, S. Ji, J. Li, D.A. Guo, M. Ye (Eds.) Secondary Metabolites identification of glycyrin and glycyrol, bioactive coumarins from licorice, Publisher, Place Published,Vol.983-984 (2015), p. 39-46.

[10] Y. Bai, L. Yin, C. Hou, Y. Zhou, F. Zhang, Z. Xu, K. Li, Y. Huang, Response Regulation for Epidermal Fabric Strain Sensors via Mechanical Strategy, in: Secondary Y. Bai, L. Yin, C. Hou, Y. Zhou, F. Zhang, Z. Xu, K. Li, Y. Huang (Eds.) Secondary Response Regulation for Epidermal Fabric Strain Sensors via Mechanical Strategy, Publisher, Place Published,Vol.33 (2023).

[11] Y.B. Ryu, J.H. Kim, S.J. Park, J.S. Chang, M.C. Rho, K.H. Bae, K.H. Park, W.S. Lee, Inhibition of neuraminidase activity by polyphenol compounds isolated from the roots of Glycyrrhiza uralensis, in: Secondary Y.B. Ryu, J.H. Kim, S.J. Park, J.S. Chang, M.C. Rho, K.H. Bae, K.H. Park, W.S. Lee (Eds.) Secondary Inhibition of neuraminidase activity by polyphenol compounds isolated from the roots of Glycyrrhiza uralensis, Publisher, Place Published,Vol.20 (2010), p. 971-974.

[12] Q.E. Wang, F.S. Lee, X. Wang, Isolation and purification of inflacoumarin A and licochalcone A from licorice by high-speed counter-current chromatography, in: Secondary Q.E. Wang, F.S. Lee, X. Wang (Eds.) Secondary Isolation and purification of inflacoumarin A and licochalcone A from licorice by high-speed counter-current chromatography, Publisher, Place Published,Vol.1048 (2004), p. 51-57.

[13] H. Liu, J. Wang, W. Zhou, Y. Wang, L. Yang, Systems approaches and polypharmacology for drug discovery from herbal medicines: an example using licorice, in: Secondary H. Liu, J. Wang, W. Zhou, Y. Wang, L. Yang (Eds.) Secondary Systems approaches and polypharmacology for drug discovery from herbal medicines: an example using licorice, Publisher, Place Published,Vol.146 (2013), p. 773-793.

[14] M. Adianti, C. Aoki, M. Komoto, L. Deng, I. Shoji, T.S. Wahyuni, M.I. Lusida, Soetjipto, H. Fuchino, N. Kawahara, H. Hotta, Anti-hepatitis C virus compounds obtained from Glycyrrhiza uralensis and other Glycyrrhiza species, in: Secondary M. Adianti, C. Aoki, M. Komoto, L. Deng, I. Shoji, T.S. Wahyuni, M.I. Lusida, Soetjipto, H. Fuchino, N. Kawahara, H. Hotta (Eds.) Secondary Anti-hepatitis C virus compounds obtained from Glycyrrhiza uralensis and other Glycyrrhiza species, Publisher, Place Published,Vol.58 (2014), p. 180-187.

[15] M. Kuroda, Y. Mimaki, Y. Sashida, T. Mae, H. Kishida, T. Nishiyama, M. Tsukagawa, E. Konishi, K. Takahashi, T. Kawada, K. Nakagawa, M. Kitahara, Phenolics with PPAR-gamma ligand-binding activity obtained from licorice (Glycyrrhiza uralensis roots) and ameliorative effects of glycyrin on genetically diabetic KK-A(y) mice, in: Secondary M. Kuroda, Y. Mimaki, Y. Sashida, T. Mae, H. Kishida, T. Nishiyama, M. Tsukagawa, E. Konishi, K. Takahashi, T. Kawada, K. Nakagawa, M. Kitahara (Eds.) Secondary Phenolics with PPAR-gamma ligand-binding activity obtained from licorice (Glycyrrhiza uralensis roots) and ameliorative effects of glycyrin on genetically diabetic KK-A(y) mice, Publisher, Place Published,Vol.13 (2003), p. 4267-4272.

[16] C. Yang, F. Li, L. Wang, W. He, B. Chen, M. Wang, Phenolic Compounds from Glycyrrhiza uralensis and their Radical-Scavenging Activity, in: Secondary C. Yang, F. Li, L. Wang, W. He, B. Chen, M. Wang (Eds.) Secondary Phenolic Compounds from Glycyrrhiza uralensis and their Radical-Scavenging Activity, Publisher, Place Published,Vol.52 (2016), p. 490-491.

[17] Y. Fu, J. Chen, Y.J. Li, Y.F. Zheng, P. Li, Antioxidant and anti-inflammatory activities of six flavonoids separated from licorice, in: Secondary Y. Fu, J. Chen, Y.J. Li, Y.F. Zheng, P. Li (Eds.) Secondary Antioxidant and anti-inflammatory activities of six flavonoids separated from licorice, Publisher, Place Published,Vol.141 (2013), p. 1063-1071.

[18] Y. Yu, S. Peng, P. Blanloeuil, S. Wu, C.H. Wang, Wearable Temperature Sensors with Enhanced Sensitivity by Engineering Microcrack Morphology in PEDOT:PSS-PDMS Sensors, in: Secondary Y. Yu, S. Peng, P. Blanloeuil, S. Wu, C.H. Wang (Eds.) Secondary Wearable Temperature Sensors with Enhanced Sensitivity by Engineering Microcrack Morphology in PEDOT:PSS-PDMS Sensors, Publisher, Place Published,Vol.12 (2020), p. 36578-36588.

[19] Y. Tang, S. Ou, L. Ye, S. Wang, Pharmacological Activities and Pharmacokinetics of Glycycoumarin, in: Secondary Y. Tang, S. Ou, L. Ye, S. Wang (Eds.) Secondary Pharmacological Activities and Pharmacokinetics of Glycycoumarin, Publisher, Place Published (2022), p. 1-13.

[20] S. Mahmoudi, M.M. Dehkordi, M.H. Asgarshamsi, Density functional theory studies of the antioxidants-a review, in: Secondary S. Mahmoudi, M.M. Dehkordi, M.H. Asgarshamsi (Eds.) Secondary Density functional theory studies of the antioxidants-a review, Publisher, Place Published,Vol.27 (2021), p. 271.

[21] Q.V. Vo, P.C. Nam, M.V. Bay, N.M. Thong, N.D. Cuong, A. Mechler, Density functional theory study of the role of benzylic hydrogen atoms in the antioxidant properties of lignans, in: Secondary Q.V. Vo, P.C. Nam, M.V. Bay, N.M. Thong, N.D. Cuong, A. Mechler (Eds.) Secondary Density functional theory study of the role of benzylic hydrogen atoms in the antioxidant properties of lignans, Publisher, Place Published,Vol.8 (2018), p. 12361.

[22] I.O. Alisi, A. Uzairu, S.E. Abechi, Molecular design of curcumin analogues with potent antioxidant properties and thermodynamic evaluation of their mechanism of free radical scavenge, in: Secondary I.O. Alisi, A. Uzairu, S.E. Abechi (Eds.) Secondary Molecular design of curcumin analogues with potent antioxidant properties and thermodynamic evaluation of their mechanism of free radical scavenge, Publisher, Place Published,Vol.44 (2020).

[23] J. Yang, J. Chen, Y. Hao, Y. Liu, Identification of the DPPH radical scavenging reaction adducts of ferulic acid and sinapic acid and their structure-antioxidant activity relationship, in: Secondary J. Yang, J. Chen, Y. Hao, Y. Liu (Eds.) Secondary Identification of the DPPH radical scavenging reaction adducts of ferulic acid and sinapic acid and their structure-antioxidant activity relationship, Publisher, Place Published,Vol.146 (2021).

[24] Z. Chen, Q. Peng, Y. Hu, Z. Liu, X. Zhao, P. Li, L. Xu, H. Zheng, F. Xue, R. Ding, X. He, Dried bonito flakes-inspired moisture-responsive actuator with a gradient structure for smart devices, in: Secondary Z. Chen, Q. Peng, Y. Hu, Z. Liu, X. Zhao, P. Li, L. Xu, H. Zheng, F. Xue, R. Ding, X. He (Eds.) Secondary Dried bonito flakes-inspired moisture-responsive actuator with a gradient structure for smart devices, Publisher, Place Published,Vol.167 (2023), p. 152-160.

[25] Y.-Z. Zheng, Z.-M. Fu, R. Guo, D.-F. Chen, Y.-C. Zhang, The important role of benzylic C H bond in the antioxidant behaviours of the xanthones, in: Secondary Y.-Z. Zheng, Z.-M. Fu, R. Guo, D.-F. Chen, Y.-C. Zhang (Eds.) Secondary The important role of benzylic C H bond in the antioxidant behaviours of the xanthones, Publisher, Place Published,Vol.103 (2021).

[26] D.H. Li, J. Guo, W. Bin, N. Zhao, K.B. Wang, J.Y. Li, Z.L. Li, H.M. Hua, Two new benzylisoquinoline alkaloids from Thalictrum foliolosum and their antioxidant and in vitro antiproliferative properties, in: Secondary D.H. Li, J. Guo, W. Bin, N. Zhao, K.B. Wang, J.Y. Li, Z.L. Li, H.M. Hua (Eds.) Secondary Two new benzylisoquinoline alkaloids from Thalictrum foliolosum and their antioxidant and in vitro antiproliferative properties, Publisher, Place Published,Vol.39 (2016), p. 871-877.

[27] F. Neese, Software update: The ORCA program system-Version 5.0, in: Secondary F. Neese (Ed.) Secondary Software update: The ORCA program system-Version 5.0, Publisher, Place Published, Vol.12 (2022).

[28] T. Lu, F. Chen, Multiwfn: a multifunctional wavefunction analyzer, in: Secondary T. Lu, F. Chen (Eds.) Secondary Multiwfn: a multifunctional wavefunction analyzer, Publisher, Place Published,Vol.33 (2012), p. 580-592.

[29] Y. Jiang, Z. Liu, N. Matsuhisa, D. Qi, W.R. Leow, H. Yang, J. Yu, G. Chen, Y. Liu, C. Wan, Z. Liu, X. Chen, Auxetic Mechanical Metamaterials to Enhance Sensitivity of Stretchable Strain Sensors, in: Secondary Y. Jiang, Z. Liu, N. Matsuhisa, D. Qi, W.R. Leow, H. Yang, J. Yu, G. Chen, Y. Liu, C. Wan, Z. Liu, X. Chen (Eds.) Secondary Auxetic Mechanical Metamaterials to Enhance Sensitivity of Stretchable Strain Sensors, Publisher, Place Published,Vol.30 (2018), p. e1706589.

[30] H. Boulebd, I. Amine Khodja, A detailed DFT-based study of the free radical scavenging activity and mechanism of daphnetin in physiological environments, in: Secondary H. Boulebd, I. Amine Khodja (Eds.) Secondary A detailed DFT-based study of the free radical scavenging activity and mechanism of daphnetin in physiological environments, Publisher, Place Published,Vol.189 (2021), p. 112831.

[31] J. Rimarčík, V. Lukeš, E. Klein, M. Ilčin, Study of the solvent effect on the enthalpies of homolytic and heterolytic N–H bond cleavage in p-phenylenediamine and tetracyano-p-phenylenediamine, in: Secondary J. Rimarčík, V. Lukeš, E. Klein, M. Ilčin (Eds.) Secondary Study of the solvent effect on the enthalpies of homolytic and heterolytic N–H bond cleavage in p-phenylenediamine and tetracyano-p-phenylenediamine, Publisher, Place Published,Vol.952 (2010), p. 25-30.

[32] T. Lu, Q. Chen, Shermo: A general code for calculating molecular thermochemistry properties, in: Secondary T. Lu, Q. Chen (Eds.) Secondary Shermo: A general code for calculating molecular thermochemistry properties, Publisher, Place Published,Vol.1200 (2021).

[33] H.A. Abuelizz, H.A.A. Taie, A.H. Bakheit, G.A.E. Mostafa, M. Marzouk, H. Rashid, R. Al-Salahi, Investigation of 4-Hydrazinobenzoic Acid Derivatives for Their Antioxidant Activity: In Vitro Screening and DFT Study, in: Secondary H.A. Abuelizz, H.A.A. Taie, A.H. Bakheit, G.A.E. Mostafa, M. Marzouk, H. Rashid, R. Al-Salahi (Eds.) Secondary Investigation of 4-Hydrazinobenzoic Acid

Derivatives for Their Antioxidant Activity: In Vitro Screening and DFT Study, Publisher, Place Published,Vol.6 (2021), p. 31993-32004.

[34] C. Sun, B. Cao, H. Yin, Y. Shi, Relationship between ESIPT properties and antioxidant activities of 5-hydroxyflavone derivates*, in: Secondary C. Sun, B. Cao, H. Yin, Y. Shi (Eds.) Secondary Relationship between ESIPT properties and antioxidant activities of 5-hydroxyflavone derivates*, Publisher, Place Published,Vol.29 (2020).

[35] S. Ninh The, T. Do Minh, T. Nguyen Van, Isoflavones and Isoflavone Glycosides: Structural-Electronic Properties and Antioxidant Relations-A Case of DFT Study, in: Secondary S. Ninh The, T. Do Minh, T. Nguyen Van (Eds.) Secondary Isoflavones and Isoflavone Glycosides: Structural-Electronic Properties and Antioxidant Relations-A Case of DFT Study, Publisher, Place Published,Vol.2019 (2019), p. 1-12.

[36] J. Hossen, M.A. Ali, S. Reza, Theoretical investigations on the antioxidant potential of a non-phenolic compound thymoquinone: a DFT approach, in: Secondary J. Hossen, M.A. Ali, S. Reza (Eds.) Secondary Theoretical investigations on the antioxidant potential of a non-phenolic compound thymoquinone: a DFT approach, Publisher, Place Published,Vol.27 (2021), p. 173.

[37] S. Kenouche, C. Sandoval-Yañez, J.I. Martínez-Araya, The antioxidant capacity of myricetin. A molecular electrostatic potential analysis based on DFT calculations, in: Secondary S. Kenouche, C. Sandoval-Yañez, J.I. Martínez-Araya (Eds.) Secondary The antioxidant capacity of myricetin. A molecular electrostatic potential analysis based on DFT calculations, Publisher, Place Published, Vol.801 (2022).

[38] K. Tayade, G.S. Yeom, S.K. Sahoo, H. Puschmann, S.B. Nimse, A. Kuwar, Exploration of Molecular Structure, DFT Calculations, and Antioxidant Activity of a Hydrazone Derivative, in: Secondary K. Tayade, G.S. Yeom, S.K. Sahoo, H. Puschmann, S.B. Nimse, A. Kuwar (Eds.) Secondary Exploration of Molecular Structure, DFT Calculations, and Antioxidant Activity of a Hydrazone Derivative, Publisher, Place Published,Vol.11 (2022).

[39] Y.Z. Zheng, G. Deng, R. Guo, D.F. Chen, Z.M. Fu, DFT Studies on the Antioxidant Activity of Naringenin and Its Derivatives: Effects of the Substituents at C3, in: Secondary Y.Z. Zheng, G. Deng, R. Guo, D.F. Chen, Z.M. Fu (Eds.) Secondary DFT Studies on the Antioxidant Activity of Naringenin and Its Derivatives: Effects of the Substituents at C3, Publisher, Place Published,Vol.20 (2019).

[40] Y.-Z. Zheng, Y. Zhou, Q. Liang, D.-F. Chen, R. Guo, C.-L. Xiong, X.-J. Xu, Z.-N. Zhang, Z.-J. Huang, Solvent effects on the intramolecular hydrogen-bond and anti-oxidative properties of apigenin: A DFT approach, in: Secondary Y.-Z. Zheng, Y. Zhou, Q. Liang, D.-F. Chen, R. Guo, C.-L. Xiong, X.-J. Xu, Z.-N. Zhang, Z.-J. Huang (Eds.) Secondary Solvent effects on the intramolecular hydrogen-bond and anti-oxidative properties of apigenin: A DFT approach, Publisher, Place Published,Vol.141 (2017), p. 179-187.

[41] S. Djafarou, H. Boulebd, The radical scavenger capacity and mechanism of prenylated coumestan-type compounds: a DFT analysis, in: Secondary S. Djafarou, H. Boulebd (Eds.) Secondary The radical scavenger capacity and mechanism of prenylated coumestan-type compounds: a DFT analysis, Publisher, Place Published,Vol.56 (2022), p. 273-281.

[42] G. Wang, Y. Liu, L. Zhang, L. An, R. Chen, Y. Liu, Q. Luo, Y. Li, H. Wang, Y. Xue, Computational study on the antioxidant property of coumarin-fused coumarins, in: Secondary G. Wang, Y. Liu, L. Zhang, L. An, R. Chen, Y. Liu, Q. Luo, Y. Li, H. Wang, Y. Xue (Eds.) Secondary Computational study on the antioxidant property of coumarin-fused coumarins, Publisher, Place Published,Vol.304 (2020), p. 125446.

[43] P.T. Thuy, P.M. Quan, D.X. Duc, N.T. Son, The antioxidative potential of procyanidin B1: DFT (density functional theory) and docking approaches, in: Secondary P.T. Thuy, P.M. Quan, D.X. Duc, N.T. Son (Eds.) Secondary The antioxidative potential of procyanidin B1: DFT (density functional theory) and docking approaches, Publisher, Place Published,Vol.28 (2022), p. 356.

[44] N.T. Son, D.T. Mai Thanh, N. Van Trang, Flavone norartocarpetin and isoflavone 2′-hydroxygenistein: A spectroscopic study for structure, electronic property and antioxidant potential using DFT (Density functional theory), in: Secondary N.T. Son, D.T. Mai Thanh, N. Van Trang (Eds.) Secondary Flavone norartocarpetin and isoflavone 2′-hydroxygenistein: A spectroscopic study for structure,

electronic property and antioxidant potential using DFT (Density functional theory), Publisher, Place Published,Vol.1193 (2019), p. 76-88.

[45] Y.Z. Zheng, D.F. Chen, G. Deng, R. Guo, Z.M. Fu, The antioxidative activity of piceatannol and its different derivatives: Antioxidative mechanism analysis, in: Secondary Y.Z. Zheng, D.F. Chen, G. Deng, R. Guo, Z.M. Fu (Eds.) Secondary The antioxidative activity of piceatannol and its different derivatives: Antioxidative mechanism analysis, Publisher, Place Published,Vol.156 (2018), p. 184-192.

[46] E. Koç, A. Üngördü, F. Candan, Antioxidant properties of methanolic extract of 'Veronica multifida' and DFT and HF analyses of its the major flavonoid component, in: Secondary E. Koç, A. Üngördü, F. Candan (Eds.) Secondary Antioxidant properties of methanolic extract of 'Veronica multifida' and DFT and HF analyses of its the major flavonoid component, Publisher, Place Published,Vol.1197 (2019), p. 436-442.

[47] S. Molaei, A.D. Tehrani, H. Shamlouei, Antioxidant activates of new carbohydrate based gallate derivatives: A DFT study, in: Secondary S. Molaei, A.D. Tehrani, H. Shamlouei (Eds.) Secondary Antioxidant activates of new carbohydrate based gallate derivatives: A DFT study, Publisher, Place Published,Vol.377 (2023).

[48] P. Huang, L.-X. Jin, J.-F. Lu, Y.-H. Gao, S.-B. Guo, A theoretical study of radical scavenging antioxidant activity of 3-styrylchromone derivatives using DFT based on quantum chemical descriptors, in: Secondary P. Huang, L.-X. Jin, J.-F. Lu, Y.-H. Gao, S.-B. Guo (Eds.) Secondary A theoretical study of radical scavenging antioxidant activity of 3-styrylchromone derivatives using DFT based on quantum chemical descriptors, Publisher, Place Published,Vol.140 (2021).

[49] H. Boulebd, DFT study of the antiradical properties of some aromatic compounds derived from antioxidant essential oils: C-H bond vs. O-H bond, in: Secondary H. Boulebd (Ed.) Secondary DFT study of the antiradical properties of some aromatic compounds derived from antioxidant essential oils: C-H bond vs. O-H bond, Publisher, Place Published,Vol.53 (2019), p. 1125-1134.