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A Quantum Chemical Study on the Antioxidant Properties of Myricetin, Quercetin, and Kaempferol Using Density Functional Theory (DFT) and Molecular Docking

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ABSTRACT

This study explores the antioxidant properties of myricetin, quercetin, and kaempferol using density functional theory (DFT) and molecular docking analyses. The findings of this study not only highlight the significant antioxidant potential of flavonoids and provide a foundation for potential clinical applications and future research aimed at optimizing their pharmacokinetic properties for therapeutic use. The optimized geometries of these flavonoids were determined through DFT calculations at the B3LYP/6-31G(d,p) level. Key electronic properties, such as total electronic energy (E_t), zero-point energy (ZPE), enthalpy (H), entropy (S), dipole moment (μ), and HOMO-LUMO energy gaps (ΔE_H-L), were computed to evaluate molecular stability and reactivity. Molecular docking with proteins 1HD2, 1RAU, 3FZS, and 3GRS revealed strong binding affinities, particularly for myricetin, which achieved docking scores of -5.330 with 1HD2 and -8.652 with 3GRS, indicating a high potential for antioxidant activity. ADME analyses demonstrated that kaempferol exhibited the most favorable pharmacokinetic profile, with a human oral absorption rate of 63.637% and compliance with Lipinski's Rule of Five. Conversely, myricetin showed reduced bioavailability despite its strong binding affinity. This work emphasizes optimizing flavonoid pharmacokinetics to maximize their therapeutic potential while reinforcing their relevance in antioxidant therapy.

Keywords: Antioxidant activity, Density functional theory (DFT), Molecular docking, Flavonoids and pharmacokinetics (ADME).

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Introduction

In the 21st century, advancing technology, environmental pollution, greenhouse effects, petrochemical products, X-UV radiation (photochemical), pharmaceuticals, and smoking have significantly increased our exposure to oxidative stress-inducing substances. These factors manifest their impact through the formation of free radicals. Additionally, biological systems constantly produce free radicals and other reactive oxygen species due to endogenous and exogenous stress factors. To protect against these stress factors, our body has an enzyme system that defends cells from oxidative damage [1-6]. The substances that enhance the effectiveness of these enzymes are known as antioxidants [7]. Antioxidants are obtained either endogenously within the body or exogenously through plants, fruits, and other foods. There are many different substances known for their antioxidant properties. Some of these are obtained through our daily diet, while the body produces others. Free radicals are molecules that attack cells and the immune system. In contrast, antioxidants are molecules that prevent the destructive effects of free radicals and inhibit chain reactions that can lead to various diseases and premature aging [8, 9].

By forming a protective shield against free radicals, antioxidants play a crucial role in preventing the chain reactions that can lead to many diseases and premature aging. The formation of these free radicals, which pose a significant risk to the body, is facilitated by petrochemical products, X and UV radiation, cigarette smoke, air pollution, and even preservatives and additives in food and beverages [10, 11]. Therefore, understanding and enhancing the role of antioxidants in our bodies is paramount in preventing these diseases [12]. Another source of free radicals is oxygen. While oxygen is essential for all vital functions, the oxygen we breathe in can also be hazardous to human health. Oxygen is necessary to release energy from food, but surrounding molecules can become oxidized during its utilization in cells. This uncontrolled production of free radicals can damage crucial cellular components such as proteins, fats, and genetic material. As cells deteriorate, a chain of chemical reactions begins, generating more free radicals [13, 14]. Moreover, as the human body ages, its antioxidant defense systems gradually weaken, and the cells' ability to repair themselves diminishes. These detrimental developments increase the risk of diseases such as cancer and heart disease [15-18]. Flavonoids are a class of polyphenolic secondary metabolites found in plants and are widely consumed in the human diet. Their basic structure, shown in Figure 1, consists of three rings commonly referred to as rings A, B, and C [19, 20].

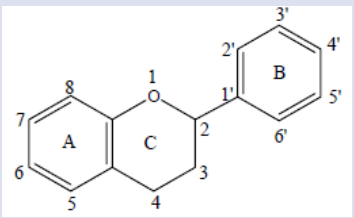

Figure 1. Basic Structure of Flavonoids

This study aims to elucidate the structural properties and activities of flavonols such as myricetin, quercetin, and kaempferol, known for their antioxidant activities, using molecular orbital methods. While significant work has been conducted on quercetin, there are fewer studies on myricetin and kaempferol and a need for more theoretical work explaining why they exhibit lower antioxidant activities. This gap in our understanding underscores the need for further research. If the relationship between these compounds can be elucidated through computational chemistry, it could guide experimental studies on newly discovered antioxidants, advancing our knowledge in this crucial area of biochemistry.

Computational chemistry plays a critical role in studying antioxidants, providing detailed insights into the molecular structure and behavior of flavonoids at the quantum mechanical level [21]. Methods such as density functional theory (DFT) allow for the precise optimization of molecular geometries and the calculation of electronic properties, stability, and reactivity. This enables the prediction of antioxidant efficiency and the identification of structural features contributing to their activity. By modeling solvent effects and exploring the impact of different substituents, computational studies can guide the design of new flavonoid derivatives with enhanced antioxidant properties, offering a cost-effective and efficient approach to advancing antioxidant research.

Computational Methods

Density Functional Theory (DFT) Study

All calculations for the compounds studied in this work were performed in the gas phase using Gaussian 2003 program [22]. The computational method utilized was Density Functional Theory (DFT), explicitly employing the closed-shell RB3LYP (Becke three-parameter hybrid functional) for non-radical species and the open-shell UB3LYP level for radicals. The basis sets used were 6-31G(d,p), which include polarization functions. Initial geometries of the compounds were generated using the GaussView 2.0 software package. The optimized geometrical structures were also obtained using the GaussView 2.0 software package [23].

Optimized geometries were determined at the B3LYP/6-31G(d,p) level for the compounds studied. Radicals were optimized at the UB3LYP/6-31G(d,p) level. The optimized geometries were verified as minimum energy structures by the absence of imaginary frequencies in the frequency calculations. Additionally, scan calculations were performed to determine the stability of the C, B, and A rings. Frequency calculations provided values for each compound's total electronic energy (E_T), internal correlation energy (E_{TC}), zero-point energy (ZPE), entropy (S), dipole moment (μ), and LUMO-HOMO energy gaps (E_{gap}). Structural parameters such as bond lengths, bond angles, and dihedral angles were also determined. Using these calculated values, the enthalpy change (ΔH) associated with OH bond dissociation, relative energy change (ΔE), Gibbs free energy change (ΔG), and LUMO-HOMO energy gaps (E_{gap})

$$E_{TC} = E_T + ZPE$$
$$E = E_T + E_{TC}$$
$$H = E + PV = E + RT$$
$$G = H - TS$$

Molecular Docking

The potential binding modes and interactions of the ligands myricetin, quercetin, and kaempferol with antioxidant proteins urate oxidase (PDB ID: 1R4U), proline-rich tyrosine kinase 2 (PDB ID: 3FZS), and glutathione reductase (PDB ID: 3GRS) were analyzed using the Maestro 14.0, Schrödinger 2024–2 software süite [24]. The three-dimensional crystal structures of these proteins were obtained from the Protein Data Bank (PDB). Before performing the docking calculations, the proteins were prepared using the Protein Preparation module in Schrödinger Maestro 14.0. This preparation process included adding hydrogen atoms, assigning partial charges, building side chains, and completing any missing loops. Water molecules located more than 3 Å away from the binding site in the crystal structures were removed. The minimized energy configurations of the protein structures were achieved using the OPLS4 force field at a physiological pH of 7.0. Flavonoids with high phenolic content exhibit superior antioxidant activities, as highlighted in studies on phenolic compound-rich foods and beverages [25, 26]. These findings underscore the importance of optimizing flavonoid structures to maximize their therapeutic potential.

The ligands were prepared for molecular docking using the LigPrep [27] tool within the Schrödinger suite, applying the OPLS4 force field at pH 7.0 ± 2.0. The receptor grid was generated by selecting any ligand atom to create the default grid box, which was set with a volumetric spacing of 20×20×20 Å for all investigated proteins. The specific coordinates used for grid generation were x: 6.63, y: 42.27, and z: 34.64 for 1HD2; x: 31.20, y: 26.88, and z: 37.99 for 1R4U; x: -3.45, y: -3.29, and z: 12.44 for 3FZS; and x: 60.72, y: 51.36, and z: 18.87 for 3GRS. This comprehensive preparation ensures that the docking studies accurately reflect the potential interactions between the ligands and the protein binding sites, thereby providing reliable insights into their binding affinities and modes of action.

ADME Study

ADME (Absorption, Distribution, Metabolism, and Excretion) properties of myricetin, quercetin, and kaempferol were calculated using the advanced QikProp [28] ool in the Schrödinger program. The QikProp module generates relevant descriptors and uses them to carry out ADME estimations, employing Jorgensen's method to obtain pharmacokinetic properties and descriptors. This use of advanced tools and methods ensures the scientific rigor of the study, giving the audience confidence in the results.

By integrating these computational techniques, this study aims to comprehensively understand the antioxidant properties of myricetin, quercetin, and kaempferol. This comprehensive understanding is supported by molecular docking and DFT calculations, ensuring the audience is well-informed and knowledgeable about the topic.

Results and Discussion

Optimized Geometries and Electronic Properties

The ability of antioxidants to neutralize free radicals depends on the stabilization of their molecular structures and the protective functions of these structures. This study evaluates the effects of intramolecular hydrogen bonding in the radical and diradical forms of myricetin, quercetin, and kaempferol. Additionally, antioxidant activities were compared considering energy parameters (ΔE, ΔH, ΔG), dipole moment (μ), and hydrogen bond lengths. In this context, the superior properties of quercetin diradical are particularly noteworthy. The molecular structure of flavonoids, particularly the number and position of hydroxyl groups, plays a pivotal role in their antioxidant activity, as demonstrated in recent studies (29, 30). These structural features enhance their ability to donate hydrogen atoms and interact with reactive oxygen species effectively.

The quercetin diradical (Qkdr/2) stands out with its high energy stability (ΔE: 72.80 kcal/mol, ΔH: 73.39 kcal/mol) and significant dipole moment (6.6901 D). The hydrogen bonds in this compound (H^1-Bond: 1.771 Å, H^2-Bond: 1.944 Å) form a strong intramolecular network that maintains the structural integrity and stability of the molecule. This robust structure allows effective interactions with free radicals, producing high antioxidant activity for the quercetin diradical. These properties make the quercetin diradical a strong candidate for combating oxidative stress. As shown in Figure 1, quercetin diradical's optimized structure and hydrogen bonding network clearly illustrate its capability to stabilize and neutralize free radicals efficiently.

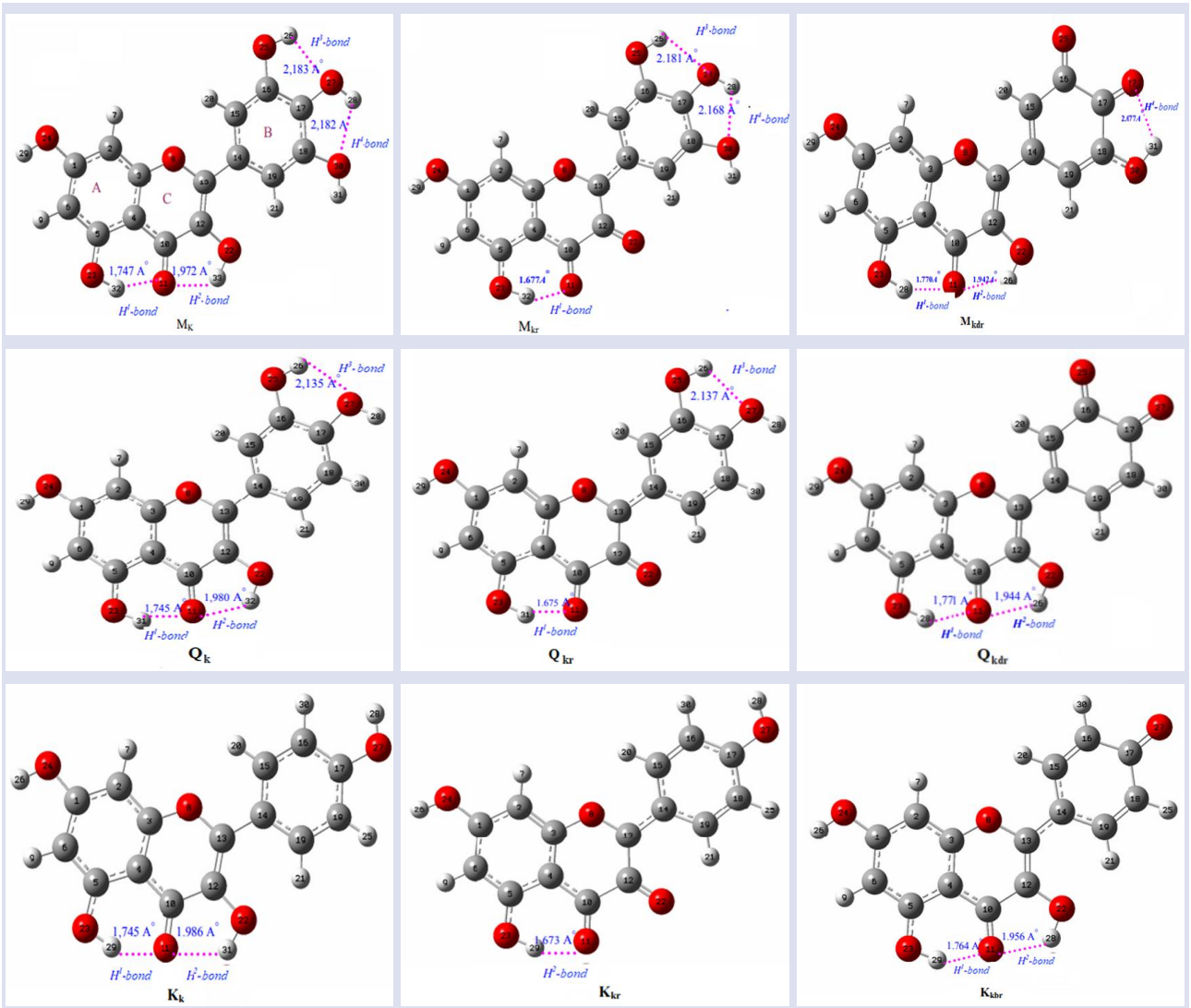

Figure 2. Optimized structures and intramolecular hydrogen bonds of myricetin, quercetin, and kaempferol and their radicals

Although the myricetin and kaempferol compounds also possess strong hydrogen bonds and good energy stability, they do not perform as well as quercetin in terms of dipole moment and the efficacy of hydrogen bonds. The myricetin radical (Mkr) and diradical (Mkdr) gain stability from their hydrogen bonds (Mkr: H^1-Bond: 1.677 Å, H^2-Bond: 2.181 Å, H^3-Bond: 2.168 Å; Mkdr: H^1-Bond: 1.770 Å, H^2-Bond: 1.942 Å, H^3-Bond: 2.118 Å), but their energy parameters and dipole moments are not as high as those of quercetin. Similarly, although kaempferol possesses strong hydrogen bonds (Kkr: H^1-Bond: 1.673 Å; Kbkr: H^1-Bond: 1.764 Å, H^2-Bond: 1.956 Å), its energy stability and dipole moment are lower compared to the other two compounds.

In conclusion, the quercetin diradical compound has the highest antioxidant activity, attributed to its high energy stability, strong intramolecular hydrogen bonds, and significant dipole moment. Myricetin ranks second with its strong hydrogen bonds and good energy stability, while kaempferol ranks third. This study highlights the critical role of intramolecular hydrogen bonding and energy parameters in antioxidant efficacy, providing valuable insights for designing new compounds. These findings offer important clues for optimizing the structure and enhancing the effectiveness of antioxidants.

The DFT calculations performed at the B3LYP/6-31G(d,p) level, have been instrumental in determining the optimized geometries of myricetin, quercetin, and kaempferol. The absence of imaginary frequencies in the vibrational analysis has unequivocally confirmed these optimized structures as minimum energy configurations. Fundamental electronic properties, including total electronic energy (E_T), zero-point energy (ZPE), entropy (S), dipole moment (μ), and LUMO-HOMO energy gaps (ΔE_{L-H}), were meticulously calculated. These properties are pivotal for understanding the intrinsic stability and reactivity of the flavonoids. The antioxidant activity of flavonoids is directly influenced by their molecular structures, particularly the number and position of hydroxyl groups, which enhance their ability to donate hydrogen atoms and neutralize free radicals effectively.

Thermodynamic Parameters

The thermodynamic parameters derived from the optimized geometries and electronic properties of myricetin, quercetin, and Kaempferol provide critical insights into their antioxidant capacities. Specifically, we have computed the enthalpy change (ΔH) associated with OH bond dissociation, relative energy change (ΔE), and Gibbs free energy change (ΔG). These parameters quantitatively measure the flavonoids' ability to donate hydrogen atoms and neutralize free radicals, which is crucial for their potential therapeutic applications.

For myricetin radical (Mkr), the enthalpy change (ΔH) is 79.44 kcal/mol, and the relative energy change (ΔE) is 78.85 kcal/mol, indicating a significant amount of energy required for OH bond dissociation. The Gibbs free energy change (ΔG) is 71.21 kcal/mol, reflecting the reaction's spontaneity. Myricetin diradical (Mkdr/2) shows slightly lower values with ΔH of 71.23 kcal/mol, ΔE of 70.51 kcal/mol, and ΔG of 63.21 kcal/mol. These values suggest that myricetin possesses substantial thermodynamic stability and effective hydrogen-donating capability, especially in its radical form.

Quercetin radical (Qkr) exhibits a ΔH of 80.14 kcal/mol and an ΔE of 79.55 kcal/mol, the highest among the studied flavonoids, indicating a robust bond dissociation energy. The ΔG value for Qkr is 71.85 kcal/mol, demonstrating its significant free energy change. The quercetin diradical (Qkdr/2) presents an enthalpy change (ΔH) of 73.39 kcal/mol, a relative energy change (ΔE) of 72.80 kcal/mol, and a Gibbs free energy change (ΔG) of 65.27 kcal/mol. The notable thermodynamic stability of quercetin, particularly in its diradical form, highlights its superior antioxidant activity, supported by its strong hydrogen-bonding network (H^1-Bond: 1.771 Å, H^2-Bond: 1.944 Å). As seen in Table 1, these values underscore quercetin's remarkable capability to stabilize and neutralize free radicals efficiently.

Kaempferol radical (Kkr) shows a ΔH of 80.22 kcal/mol and a ΔE of 79.63 kcal/mol, with a Gibbs free energy change (ΔG) of 71.86 kcal/mol, suggesting high energy stability. The Kaempferol B-ring radical (Kbkr) displays an enthalpy change (ΔH) of 80.66 kcal/mol, a relative energy change (ΔE) of 80.07 kcal/mol, and a Gibbs free energy change (ΔG) of 72.39 kcal/mol. These values indicate that Kaempferol has substantial antioxidant potential, albeit slightly lower than quercetin, due to its energy parameters and hydrogen-bond lengths (H^1-Bond: 1.764 Å, H^2-Bond: 1.956 Å). Energy parameters such as ΔE, ΔH, and ΔG play a critical role in determining the antioxidant capacity of flavonoids, with lower ΔH and ΔG values corresponding to higher hydrogen-donating capabilities and stability against oxidative stress [31, 32].

In conclusion, the thermodynamic parameters reveal that quercetin, particularly in its diradical form (Qkdr/2), exhibits the highest antioxidant activity due to its superior energy stability and strong intramolecular hydrogen bonding. Myricetin follows, demonstrating significant hydrogen-donating capability and thermodynamic stability, especially in its radical form. Kaempferol ranks third while showing considerable antioxidant potential due to slightly lower energy stability and dipole moments. These findings provide valuable insights for designing new antioxidant compounds with enhanced stability and efficacy for therapeutic applications.

Table 1. Thermodynamic parameters and intramolecular hydrogen bonding lengths of myricetin, quercetin, and kaempferol, and their radicals

Comp.	ΔE	ΔH	ΔG	μ	Δ_{L+H}	H^1-Bond	H^2-Bond	H^3-Bond	H^4-Bond	H^5-Bond
Mkr	78.85	79.44	71.21	3.6225	5.49	1.677	-	-	2.181	2.168
Mkdr/2	70.51	71.23	63.21	5.1623	6.61	1.770	1.942	2.118	-	-
Qkr	79.55	80.14	71.85	4.9893	6.12	1.675	-	2.137	-	-
Qkdr/2	72.80	73.39	65.27	6.6901	6.99	1.771	1.944	-	-	-
Kkr	79.63	80.22	71.86	6.9160	6.06	1.673	-	-	-	-
Kbkr	80.07	80.66	72.39	5.5238	6.40	1.764	1.956	-	-	-

To investigate the antioxidant activities of myricetin, quercetin, and kaempferol, we first determined the optimized structures of these compounds based on the structural parameters obtained from calculations. Upon examining the optimized geometric structures of these compounds, it is evident that the only structural difference lies in the number of hydroxyl groups on the B-ring. Myricetin has 3 OH groups, quercetin has 2 OH groups, and kaempferol has 1 OH group. According to the literature, the TEAC values for myricetin, quercetin, and kaempferol are 3.10, 4.70, and 1.34, respectively [33]. If there were a direct relationship between the number of hydroxyl groups and antioxidant activity, myricetin, with the most OH groups, would be expected to have the highest TEAC value.

Conversely, if having fewer OH groups resulted in higher antioxidant activity, kaempferol would have the highest TEAC value. However, quercetin has the highest TEAC value among the three. Therefore, there is no direct relationship between the number of OH groups and the TEAC value. These compounds exhibit antioxidant properties due to their ability to scavenge free radicals. As these compounds exhibit this effect, they donate hydrogen to free radicals, forming radicals and diradicals. These radicals can form chelate rings with trace metals present in our bodies, facilitating the easy release of hydrogen atoms, as shown in Figure 3. The released hydrogen atoms then bind to free radicals, neutralizing them [33]. As illustrated in Figure 4, the reactivity (energy) of the formed diradicals is crucial; the higher their reactivity, the stronger the chelate ring they create, thus enhancing their antioxidant capacity.

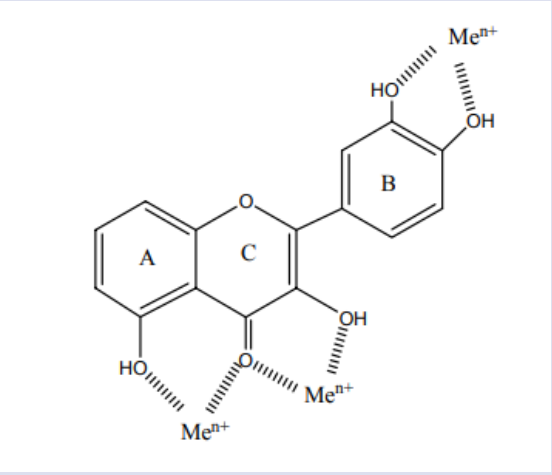

Figure 3. Chelation of trace metals

Additionally, to investigate the antioxidant activities of myricetin, quercetin, and kaempferol, we first determined the optimized structures of these compounds based on the structural parameters obtained from calculations. Upon examining the optimized geometric structures of these compounds, it is evident that the only structural difference lies in the number of hydroxyl groups on the B-ring. Myricetin has 3 OH groups, quercetin has 2 OH groups, and kaempferol has 1 OH group. According to the literature, the TEAC values for myricetin, quercetin, and kaempferol are 3.10, 4.70, and 1.34, respectively [34]. If there were a direct relationship between the number of hydroxyl groups and antioxidant activity, myricetin, with the most OH groups, would be expected to have the highest TEAC value.

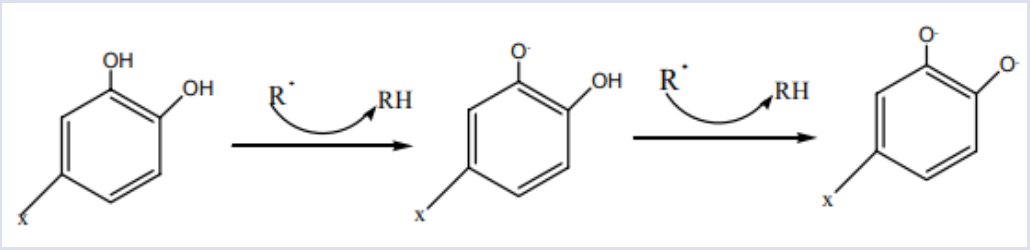

Figure 4. Scavenging of Reactive Free Radicals by Flavonoids

Conversely, if having fewer OH groups resulted in higher antioxidant activity, kaempferol would have the highest TEAC value. However, quercetin has the highest TEAC value among the three. Therefore, there is no direct relationship between the number of OH groups and the TEAC value. Among the flavonoids studied, quercetin's superior antioxidant activity is attributed to its optimal balance of electronic properties and strong hydrogen bonding network, highlighting its potential as a leading antioxidant candidate for therapeutic applications.

Molecular Docking

This study investigates the antioxidant properties of Myricetin, Quercetin, and Kaempferol, offering a comprehensive evaluation through molecular docking and ADME (Absorption, Distribution, Metabolism, and Excretion) analyses. In the molecular docking analysis, the interactions of these flavonoids with four specific proteins—1HD2, 1R4U, 3FZS, and 3GRS—were meticulously examined. The results indicate that Myricetin possesses the highest binding affinity among all the tested proteins. Notably, Myricetin achieved shallow docking scores of -5.330 with 1HD2 and an impressive -8.652 with 3GRS, underscoring its robust binding properties. These findings strongly suggest that Myricetin forms stable interactions with the active sites of these proteins, demonstrating a high potential for antioxidant activity.

As illustrated in Figure 5, the detailed 3D visualization of the docking interactions between these flavonoids and

the respective proteins provides further insight into their binding modes. Each row of the figure represents a different protein (1HD2, 1R4U, 3FZS, and 3GRS), while each column shows the binding of Quercetin, Kaempferol, and Myricetin, respectively. The colorful representations highlight the complex interactions within the protein active sites, showcasing how Myricetin, Quercetin, and Kaempferol are positioned and stabilized. The figure vividly demonstrates Myricetin's superior binding affinity, particularly with 3GRS, where the intricate binding network is visible. These visualizations are crucial for understanding the molecular mechanisms that underpin the high docking scores and the potential antioxidant efficacy of these compounds.

Further emphasizing the robustness of these interactions, Figure 6 presents a detailed 2D visualization of the interactions between the receptor regions of the target proteins and the studied compounds. This figure highlights the specific binding modes and critical interactions, such as hydrogen bonds and hydrophobic contacts that these flavonoids form with the proteins. The visualization clearly shows the interaction sites and the nature of the interactions, providing insights into the molecular mechanisms underpinning the high docking scores. Such detailed interaction maps are crucial for understanding how these compounds stabilize within the protein active sites, facilitating their antioxidant action.

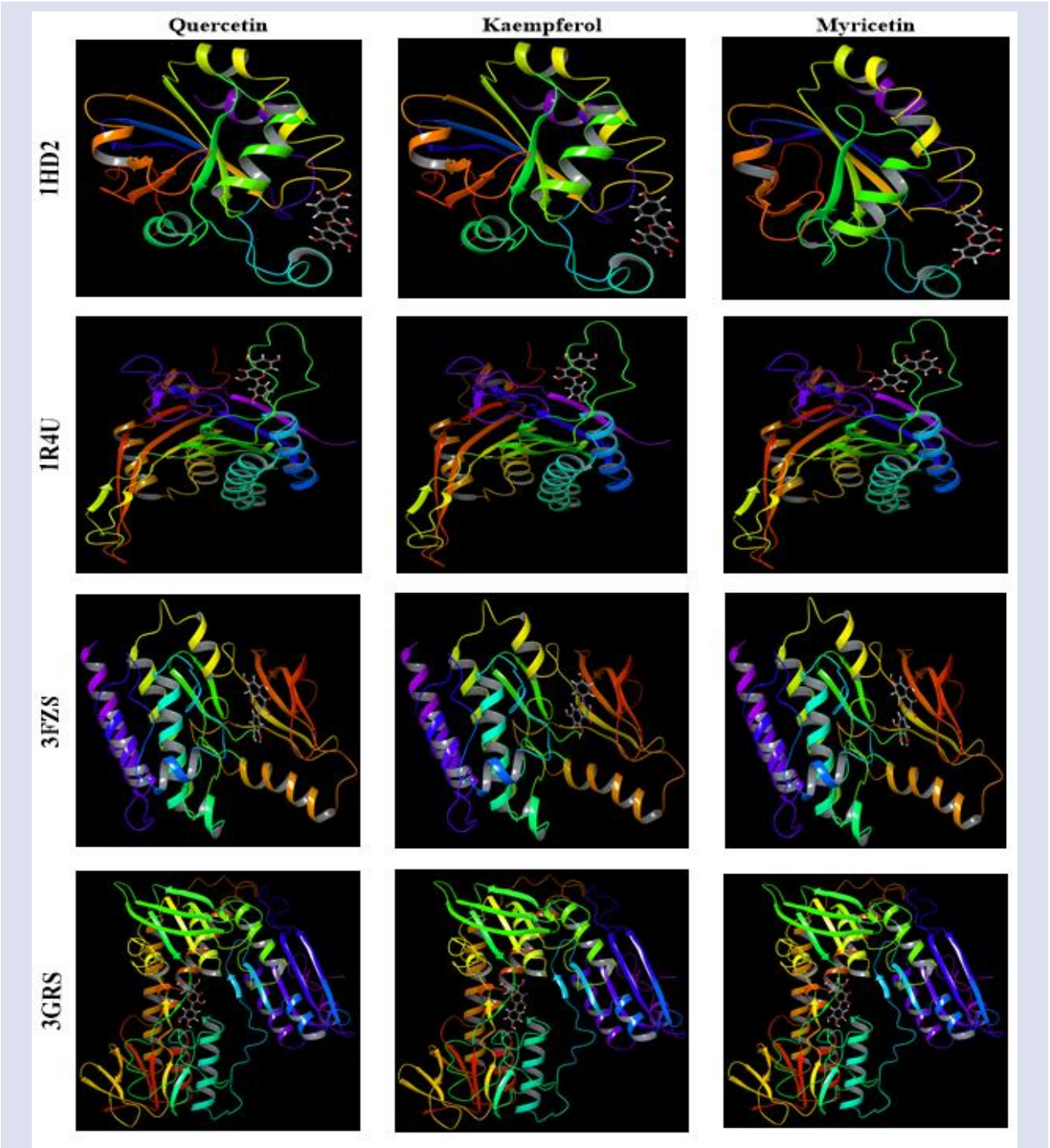

Figure 5. 3D demonstration of docking the mentioned antioxidant proteins with the ligands.

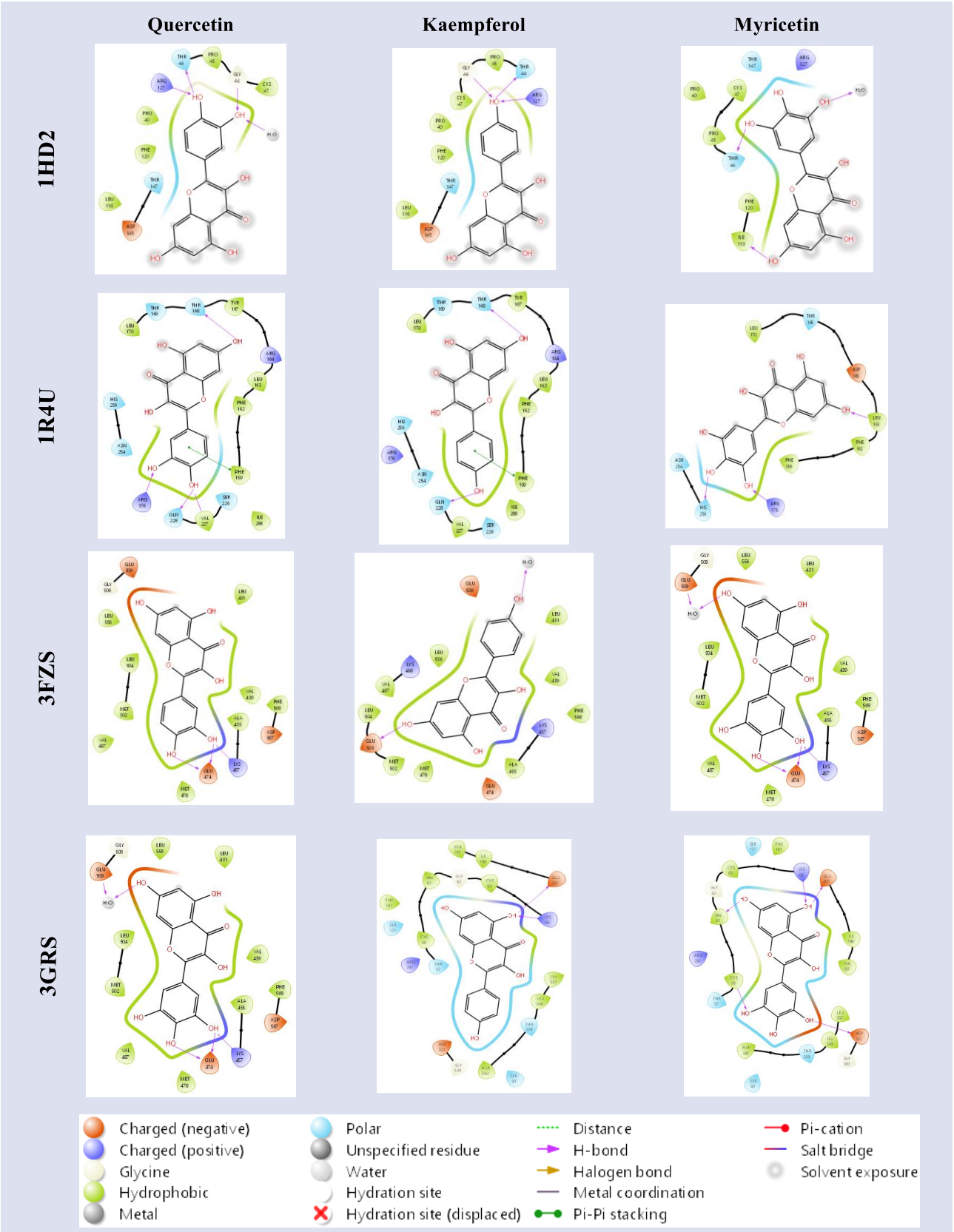

Figure 6. 2D presentation of the interaction between the receptor region of the target protein with the studied compounds.

As seen in Table 2, Myricetin consistently showed the highest docking scores compared to Quercetin and Kaempferol across all tested proteins, reinforcing its potential as a strong antioxidant agent. This superior performance is due to Myricetin's robust binding properties, which enable it to form stable interactions with the active sites of these proteins. The high docking scores of Myricetin, particularly with proteins 1HD2 and 3GRS, underscore its ability to bind and stabilize within the protein structures effectively. These stable

interactions are crucial for neutralizing free radicals, thereby protecting cells from oxidative stress and contributing to Myricetin's high potential for antioxidant activity. The detailed interaction maps in Figures 1 and 2 illustrate how Myricetin fits into the protein binding sites, forming critical hydrogen bonds and hydrophobic contacts that enhance its binding affinity. This strong binding capability, combined with its potential for effective free radical neutralization, makes Myricetin a promising candidate for further research and development in antioxidant therapies.

Table 2. The docking results obtained from interaction of the quercetin, kaempferol, and myricetin ligands with the mentioned proteins

Protein	Ligand	Docking score	Glide hbond	Glide emodel	Glide ligand efficiency	Glide energy
1HD2	Quercetin	-4.427	0.000	-39.799	-0.201	-32.473
	Kaempferol	-4.324	-0.618	-34.030	-0,206	-27,642
	Myricetin	-5.330	-0.312	-39.985	-0.232	-33.166
1R4U	Quercetin	-5.130	-0.304	-38.596	-0.233	-30.473
	Kaempferol	-5.207	-0.778	-40.067	-0.248	-31.606
	Myricetin	-4.363	0.000	-40.203	-0.190	-32.843
3FZS	Quercetin	-6.953	0.000	-55.423	-0.316	-38.505
	Kaempferol	-7.544	-0.335	-57.252	-0.359	-40.407
	Myricetin	-6.895	0.000	-59.023	-0.300	-40.893
3GRS	Quercetin	-8.206	-0.320	-79.799	-0.373	-54.510
	Kaempferol	-8.206	-0.320	-79.799	-0.373	-54.510
	Myricetin	-8.652	-0.297	-71.841	-0.376	-48.929

ADME Analysis

The ADME analysis reveals critical insights into the pharmacokinetic profiles of Myricetin, Quercetin, and Kaempferol, which are essential for assessing their suitability as therapeutic agents. Kaempferol stands out with the most favorable pharmacokinetic properties, exhibiting the highest human oral absorption rate at 63.637% and full compliance with Lipinski's Rule of Five, indicating excellent potential for effective absorption and utilization in the human body. Quercetin shows moderate absorption at 51.649%, making it a viable candidate for further development. In contrast, Myricetin, despite its superior binding affinity in molecular docking studies, has the lowest human oral absorption rate at 26.816%, highlighting potential limitations in its bioavailability and necessitating optimization to harness its therapeutic potential fully.

Moreover, the analysis of molecular properties such as dipole moment, hydrogen bond donors and acceptors, and partition coefficient (QPlogPo/w) underscores the nuanced pharmacokinetic behaviors of these flavonoids. Myricetin's high dipole moment (6.539) and maximum hydrogen bond interactions contribute to its robust binding properties but may also influence its lower lipophilicity and absorption. Kaempferol achieves a superior pharmacokinetic profile with its favorable QPlogPo/w (1.041) and optimal balance of hydrogen bonding properties. Quercetin's moderate properties align with its satisfactory absorption rates. The antioxidant properties of flavonoids derived from natural sources, such as dandelion and hibiscus, demonstrate their broad applicability in functional foods and pharmaceuticals [35]. Their bioavailability and pharmacokinetic behaviors warrant further investigation to enhance their therapeutic efficacy.The comprehensive integration of docking and ADME results underscore the importance of Kaempferol and Quercetin as promising therapeutic candidates while indicating that enhancing Myricetin's pharmacokinetic characteristics could significantly improve its therapeutic efficacy.

Table 3. Pharmacokinetic and ADME Parameters of the Investigated Ligands

Ligand	Dipole	Mol MW	Donor HB	Accpt HB	QPlogPo/w	No. of meta	QPlogKhsa	Rule of Five	% Human oral absorption
Quercetin	4.721	302.240	4.000	5.250	0.367	5	-0.343	0	51.649
Kaempferol	4.456	286.240	3.000	4.500	1.041	4	-0.191	0	63.637
Myricetin	6.539	318.239	5.000	6.000	-0.299	6	-0489	1	26.816
Recommended	1–12.5	130–725	0–6	2–20	-2–6.5	1–8	-1.5–1.5	Max 4	> 80% is high < 25% is poor

This study investigates the antioxidant properties of Myricetin, Quercetin, and Kaempferol, offering a comprehensive evaluation through molecular docking and ADME (Absorption, Distribution, Metabolism, and Excretion) analyses. In the molecular docking analysis, the interactions of these flavonoids with four specific proteins—1HD2, 1R4U, 3FZS, and 3GRS—were meticulously examined. The results indicate that Myricetin possesses the highest binding affinity among all the tested proteins. Notably, Myricetin achieved shallow docking scores of -5.330 with 1HD2 and an impressive -8.652 with 3GRS, underscoring its robust binding properties. These findings strongly suggest that Myricetin forms stable interactions with the active sites of these

proteins, demonstrating a high potential for antioxidant activity.

Further emphasizing the robustness of these interactions, Figure 2 presents a detailed 2D visualization of the interactions between the receptor regions of the target proteins and the studied compounds. This figure highlights the specific binding modes and critical interactions, such as hydrogen bonds and hydrophobic contacts that these flavonoids form with the proteins. The visualization clearly shows the interaction sites and the nature of the interactions, providing insights into the molecular mechanisms underpinning the high docking scores. Such detailed interaction maps are crucial for understanding how these compounds stabilize within the protein active sites, facilitating their antioxidant action. These findings underline the importance of exploring structural modifications to flavonoids, such as optimizing the hydroxyl group arrangement and enhancing pharmacokinetic properties, to develop more potent and bioavailable antioxidant therapies.

The ADME analyses provide crucial insights into the pharmacokinetic profiles of Myricetin, Quercetin, and Kaempferol. Kaempferol is a promising candidate for therapeutic applications, given its favorable pharmacokinetic properties, including a high percentage of human oral absorption at 63.637% and full compliance with Lipinski's Rule of Five. In contrast, Myricetin, despite its superior binding affinity, shows a lower human oral absorption rate of 26.816%, indicating potential limitations in its bioavailability. Quercetin, with a human oral absorption rate of 51.649%, displays moderate pharmacokinetic properties. These findings underscore the need to optimize Myricetin's pharmacokinetic properties to harness its therapeutic potential fully. The comprehensive analysis of docking and ADME results underscores the importance of these flavonoids in antioxidant therapy, providing valuable information for future research.

Structural modifications to flavonoids, including optimizing hydroxyl group positions and enhancing phenolic content, are crucial for improving antioxidant efficacy, as evidenced by recent findings [25, 36]. Future research should focus on these aspects to fully harness the therapeutic potential of these compounds.

Conclusion

The comprehensive evaluation of myricetin, quercetin, and kaempferol through DFT calculations and molecular docking has provided valuable insights into their antioxidant properties. Myricetin exhibited the highest binding affinity in docking studies, underscoring its robust interaction with protein active sites and potential as a strong antioxidant agent. Table 1 shows quercetin demonstrated the highest antioxidant activity with its superior thermodynamic stability and significant dipole moment, especially in its diradical form (Qkdr/2). This finding emphasizes the critical role of energy stability and intramolecular hydrogen bonding in enhancing antioxidant efficacy. While showing substantial antioxidant potential, kaempferol ranked third due to its lower energy stability and dipole moment than quercetin and myricetin. In conclusion, quercetin is the most potent antioxidant among the three flavonoids studied, followed by myricetin and Kaempferol. The study underscores the need for further research to optimize the pharmacokinetic properties of these compounds, particularly myricetin, to exploit their therapeutic potential fully. These findings contribute to the ongoing efforts to design new antioxidant compounds with enhanced stability and efficacy, providing a foundation for future experimental and theoretical investigations in antioxidant research.

Conflicts of interest

There are no conflicts of interest in this work.

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