


 Cite this: *RSC Adv.*, 2022, 12, 32693

The radical scavenging activity of glycozolidol in physiological environments: a quantum chemical study†

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Glycozolidol was isolated from the root of *Glycosmis pentaphylla* (6-hydroxy-2-methoxy-3-methylcarbazole, GLD). This molecule attracted considerable interest due to its beneficial biological activities that likely stem from its antioxidant activity; yet, the radical scavenging action of GLD has not been investigated thus far. In this study, DFT calculations were used to estimate the radical scavenging activity of GLD against a variety of biologically significant radical species in physiological environments. The findings demonstrated that GLD exerts significant antiradical activity in water at pH = 7.40 and in pentyl ethanoate (as a model of lipidic media) with $k_{\text{overall}} = 8.23 \times 10^6$ and $3.53 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, respectively. In aqueous solution, the sequential proton-loss electron transfer mechanism made the highest contribution to the activity, whereas in nonpolar solvents the formal hydrogen transfer mechanism dominated the activity. GLD is predicted to have strong antiradical activity against $\text{CH}_3\text{O}^\bullet$, $\text{CH}_3\text{OO}^\bullet$, $\text{CCl}_3\text{OO}^\bullet$, NO_2 , $\text{SO}_4^{\bullet-}$, DPPH and $\text{ABTS}^{+\bullet}$ $k_{\text{app}} \approx 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $k_f \approx 10^6 \text{ M}^{-1} \text{ s}^{-1}$. The results suggest that GLD is a good radical scavenger in physiological environments.

 Received 19th September 2022
 Accepted 8th November 2022

DOI: 10.1039/d2ra05907j

rsc.li/rsc-advances

1. Introduction

Antioxidants attract considerable interest owing to their roles in important biological processes, and therefore their preferential inclusion in food and pharmaceutical products.^{1,2} They protect against oxidative deterioration in the body and thus against oxidative stress-induced pathological processes such as cancer, aging, hypo sexuality, hyperlipidemia, cardiovascular disease, inflammation, and many others.^{1,3,4}

It is estimated that more than 10 000 individual phytochemicals have been identified in plants, including polysaccharides, phenolics, triterpenoids, steroids, carotenoids, vitamins, essential oils, and alkaloids. Among the great structural diversity of phytochemicals, alkaloid components have attracted considerable attention for known or suspected activity in treating various diseases.^{4,5} Thus, highly substituted carbazole alkaloids are active against *e.g.* neurodegenerative diseases, cancer, tuberculosis and Human Immunodeficiency Virus

infections.^{6,7} Among these compounds, glycozolidol (6-hydroxy-2-methoxy-3-methylcarbazole) (Fig. 1) was isolated from the roots of *Glycosmis pentaphylla* and since confirmed to exert antibacterial (against both Gram-positive and Gram-negative bacteria) and antifungal activities.^{8,9} Glycozolidol belongs to a class of natural aromatic nitrogen heterocyclic alkaloids. Based on the oxygenation pattern of tricyclic carbazole alkaloids, glycozolidol could provide robust antioxidant activity due to the presence of amine and quinone groups, however, there are no reports on the mechanism and/or kinetics of the radical scavenging activity of glycozolidol. Herein, we explore the effects of solvent environments and molecular structures on the antioxidant activity and oxidation resistance of glycozolidol against a range of free radicals by using thermodynamic and kinetic calculations.

2. Computational details

All density functional theory (DFT) computations in this work were performed with the Gaussian 16 suite of programs¹⁰ using

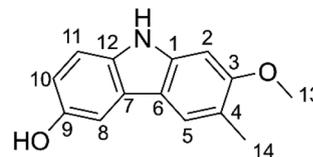


Fig. 1 Chemical structure of glycozolidol (GLD).

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 † Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d2ra05907j>


the M06-2X functional and the 6-311++G(d,p) basis set.¹¹ The M06-2X functional is one of the most reliable methods for computing the thermodynamics and kinetics of radical reactions.^{12,13} This method is often used to evaluate the radical scavenging activity of natural and synthesized compounds^{12,14-17} due to its reliable predictions when compared to experimental data.¹⁸⁻²² The solvent effects of water and pentyl ethanoate were predicted using the SMD technique,²³ following a well-established practice in modelling the radical scavenging activity of antioxidants.^{12,21,24}

The proton affinity (PA), bond dissociation enthalpy (BDE), and ionization energy (IE) values were calculated as follows.²¹

$$\text{PA} = \text{H}(\text{GLD}^-) + \text{H}(\text{H}^+) - \text{H}(\text{GLD-H}) \quad (1)$$

$$\text{BDE} = \text{H}(\text{GLD}^\cdot) + \text{H}(\text{H}^\cdot) - \text{H}(\text{GLD-H}) \quad (2)$$

$$\text{IE} = \text{H}(\text{GLD-H}^{+\cdot}) + \text{H}(\text{e}^-) - \text{H}(\text{GLD-H}) \quad (3)$$

where H(e), H(H⁺), H(H[·]), H(GLD-H^{·+}), H(GLD⁻), H(GLD[·]), and H(GLD-H) are the relative enthalpies of the electron, proton, hydrogen atom, cation-radical, anion, radical and neutral molecule, respectively.

The quantum mechanics-based test for overall free radical scavenging activity (QM-ORSA) protocol²⁰ was used to complete the kinetic calculations. The rate constants (*k*) were calculated using conventional transition state theory (TST) at 1 M standard state, 298.15 K, following eqn (4).^{21,25-31}

$$k = \sigma_K \frac{k_B T}{h} e^{-(\Delta G^\ddagger)/RT} \quad (4)$$

where *s* is the reaction symmetry number,^{32,33} *k* stands for tunneling corrections that were calculated using Eckart barrier,³⁴ *k_B* is the Boltzmann constant, *h* is the Planck constant, ΔG^\ddagger is Gibbs free energy of activation.

The Marcus theory was used to calculate the reaction barriers of single electron transfer (SET) reactions in media.^{35,36} The eqn (5) and (6) were used to compute the Gibbs free energy change of reaction ΔG^\ddagger for the SET reaction.

$$\Delta G_{\text{SET}}^\ddagger = \frac{\lambda}{4} \left(1 + \frac{\Delta G_{\text{SET}}^0}{\lambda} \right)^2 \quad (5)$$

$$\lambda \approx \Delta E_{\text{SET}} - \Delta G_{\text{SET}}^0 \quad (6)$$

Where ΔG_{SET}^0 represents the conventional Gibbs free energy change of the reaction and ΔE represents the nonadiabatic energy difference between reactants and vertical products for SET.^{37,38}

For rate constants around the diffusion limit, a modification was made.²⁰ Collins–Kimball theory was used to calculate the apparent rate constants (*k_{app}*) for an irreversible bimolecular diffusion-controlled reaction in solvents at 298.15 K,³⁹ and the literature was used to estimate the steady-state Smoluchowski rate constant (*k_D*).^{20,40}

$$k_{\text{app}} = \frac{k_{\text{TST}} k_{\text{D}}}{k_{\text{TST}} + k_{\text{D}}} \quad (7)$$

$$k_{\text{D}} = 4\pi R_{\text{AB}} D_{\text{AB}} N_{\text{A}} \quad (8)$$

$D_{\text{AB}} = D_{\text{A}} + D_{\text{B}}$ (denotes the mutual diffusion coefficient of A and B),^{39,41} where *D_A* or *D_B* is obtained using the Stokes–Einstein formulation eqn (9).^{42,43}

$$D_{\text{A or B}} = \frac{k_{\text{B}} T}{6\pi\eta a_{\text{or B}}} \quad (9)$$

η is the viscosity of the solvents (*i.e.* η (pentyl ethanoate) = 8.62×10^{-4} Pa s, η (H₂O) = 8.91×10^{-4} Pa s) and *a* is the radius of the solute.

The existence of just one imaginary frequency served as a distinguishing feature across all of the transition stages. Intrinsic coordinate calculations were carried out to ensure that each transition state has an accurate connection to both the pre- and post-complexes.

To avoid over-penalizing entropy losses in solution, Okuno's corrections were applied,⁴⁴ which were then updated with the free volume theory utilizing the Benson correction.^{20,45-47}

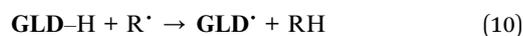
Values for *pK_a* are computed in accordance with Galano *et al.* $pK_{\text{a}} = m\Delta G_{(\text{BA})} + C_0$, where *m* and *C₀* are fitted parameters taken directly from ref. 48 (the M06-2X/6-311++G(d,p) approach), and $\Delta G_{(\text{BA})}$ is the difference in Gibbs free energy between the conjugated base (B) and the corresponding acid (A).

3. Results and discussion

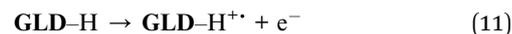
3.1 The thermodynamic study

The GLD (GLD-H) can react with free radicals (R[·]) *via* either of the three main pathways:

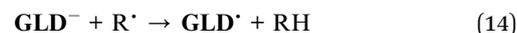
- Formal hydrogen transfer (FHT)^{21,49,50}



- Sequential electron transfer–proton transfer (SETPT)^{51,52}



- Sequential proton loss electron transfer (SPLET)⁵²⁻⁵⁵



In the initial step, the characteristic thermodynamic parameters (BDE, PA, IE) that define the energy barrier of the first step of each mechanism were calculated for all bonds in the HOO[·] radical scavenging activity of GLD in the gas phase (the standard medium for computational chemistry), in pentyl ethanoate for a lipid medium, and in water at pH 7.4 for an aqueous physiological environment. Table 1 provides an overview of the findings.

The BDEs ranged from 82.8 to 141.9 kcal mol⁻¹, whereas the PA and IE values were in the range of 84.7–343.6 and 99.2–165.2



Table 1 The computed thermodynamic parameters (BDE, PA, IE in kcal mol⁻¹) of GLD in the studied media (G: the gas phase; P: pentyl ethanoate; W: water)

Positions	BDE			PA			IE		
	G	P	W	G	P	W	G	P	W
C2-H	136.7	116.0	132.0				165.2	122.1	99.2
C5-H	114.4	114.9	115.3						
C8-H	115.6	116.3	129.2						
C10-H	116.6	138.6	116.7						
C11-H	141.9	115.9	132.8						
C13-H	99.9	101.4	101.9						
C14-H	92.7	92.8	92.6						
O9-H	85.2	83.1	82.8	343.6	116.2	84.7			
N-H	91.6	92.5	90.4						

kcal mol⁻¹, respectively. The BDE values varied somewhat randomly, while the PAs and IEs reduced in correlation to the dielectric constant of solvents. The lowest BDE of C-H bond was observed at C14-H (BDE = 92.7, 92.8 and 92.6 kcal mol⁻¹ in the gas phase, pentyl ethanoate and water, respectively) that is still higher than BDEs of N-H and O9-H by about 0.3–9.8 kcal mol⁻¹. The lowest BDE was found at the O9-H bond (85.2, 83.1 and 82.8 kcal mol⁻¹ in the gas phase, pentyl ethanoate and water, respectively). The SPLET and SETPT mechanisms are not favorable in the gas phase or pentyl ethanoate solvent due to the higher PA and IE values compared with the BDE(O9-H). Thus it is expected that the O9-H bond will play a dominant role in the radical scavenging activity of GLD following the FHT reaction in all of the studied media; however, in the aqueous solution, the

Table 2 The computed ΔG^0 (in kcal mol⁻¹) of the HOO[•] + GLD following the formal hydrogen transfer (FHT), proton loss (PL) and single electron transfer (SET) reactions in the studied media (G: the gas phase; P: pentyl ethanoate; W: water)

Positions	FHT			PL			SET		
	G	P	W	G	P	W	G	P	W
C2-H	48.3	25.8	41.3				143.1	60.7	54.3
C5-H	24.4	25.9	23.7						
C8-H	26.5	26.5	38.6						
C10-H	27.2	51.5	25.2						
C11-H	53.1	27.1	42.0						
C13-H	10.9	12.9	10.6						
C14-H	4.1	4.8	1.7						
O9-H	-3.6	-4.3	-7.3	188.4	130.2	89.3			
N-H	3.0	3.7	0.1						

SPLET mechanism may have a major contribution in the radical scavenging activity if the spontaneous dissociation of the acidic protons eliminates the energy barrier of the first step.

The Gibbs free energies of the GLD + HOO[•] reaction following the proton loss (PL-the first step of SPLET), the FHT, and single electron transfer (SET-the first step of SETPT) mechanisms were calculated in order to eliminate pathways that are not spontaneous thermodynamically, and rate constants were only calculated for the spontaneous reactions. The results are shown in Table 2. The results showed that the process was spontaneous only according to the FHT mechanism, especially at the O9-H bond ($\Delta G^0 = -7.3$ to -3.6 kcal mol⁻¹). The ΔG^0 values of the H-abstraction of the N-H bond were 3.0, 3.7 and 0.1 kcal mol⁻¹ in the gas phase, pentyl ethanoate and water, respectively, while the lowest ΔG^0 for the C-H bonds was observed at the C14-H bond with 4.1, 4.8 and 1.7 kcal mol⁻¹ in the gas phase, pentyl ethanoate and water, respectively. The FHT reactions of the other C-H bonds were not spontaneous ($\Delta G^0 = 10.6$ –53.1 kcal mol⁻¹). Similarly, neither the proton loss nor SET reactions were spontaneous in any of the investigated solvents. Thus, in nonpolar environments the HOO[•] radical scavenging activity follows the FHT pathway, however in polar media such as water at pH = 7.40, the deprotonation of GLD needs also be addressed.

3.2 The kinetic study

3.2.1. Acid-base equilibrium. The conjugate base form often exhibits much higher activity than the protonated form of acidic species in aqueous environments.^{12,17} To identify the most probable radical scavenging activity, the protonation state of GLD was initially examined at physiological pH. The GLD structure permits protonation at the N-H and O9-H bonds in accordance with reactions (1) and (2); hence, the pK_a values of GLD were determined based on the published literature⁴⁸ and are depicted in Fig. 2.



The computed pK_a values for the amine were pK_{a1} = -2.56 (for the cation form of the N-H bond) and pK_{a2} = 10.64 (for the O9-H bond). In an aqueous solution with a pH of 7.4, GLD exists in two states: neutral (HA, 99.9%) and anion (A⁻, 0.1%). As a consequence of this, both states were considered during the kinetic analysis of the HOO[•] radical activity of GLD in water

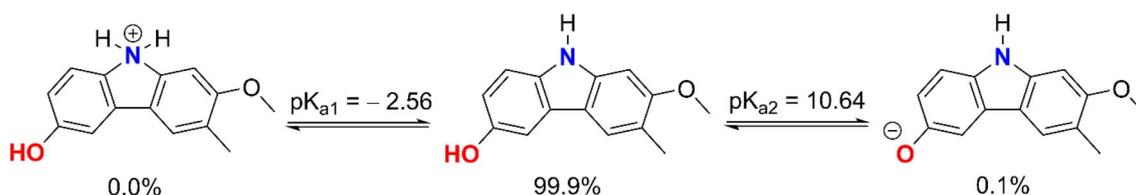
**Fig. 2** Possible protonation states of GLD at pH = 7.40.

Table 3 Computed ΔG^\ddagger in kcal mol⁻¹, tunneling correction (κ), Γ in %, and k_{Eck} , k_{app} , k_f , and k_{overall} in M⁻¹ s⁻¹ of GLD + HOO[•] reactions

Solv.	Mechanisms	ΔG^\ddagger	κ	k_{Eck}	k_{app}	k_f^a	k_{overall}	Γ
G	FHT N-H	15.8	570.5	9.64×10^3			8.53×10^5	1.1
	FHT O9-H	12.0	82.3	8.43×10^5				98.9
P	FHT N-H	18.8	2915		2.90×10^2		3.53×10^4	0.8
	FHT O9-H	13.8	76.4		3.50×10^4			99.2
W	SET (A ⁻)	1.6	15.3 ^b		7.90×10^9	7.90×10^6	8.23×10^6	96.0
	FHT N-H	17.6	4218		3.04×10^3	3.03×10^4		0.0
	(HA) O9-H	12.8	116.5		3.30×10^5	3.30×10^5		4.0

^a $k_f = f \cdot k_{\text{app}}$; $f(\text{A}^-) = 0.001$, $f(\text{HA}) = 0.999$. ^b The nuclear reorganization energy (λ , in kcal mol⁻¹).

at a pH value of 7.4, whereas in nonpolar media (*i.e.* the gas phase and pentyl ethanoate) the neutral state was used to compute the rate constants of the HOO[•] + GLD reaction.

3.2.2. The kinetic study. The thermodynamic calculations (Tables 1 and 2) showed that the HOO[•] antiradical activity of GLD in the nonpolar media is dominated by the hydrogen transfer reaction of the N-H and O9-H bonds ($\Delta G^0 \approx 0$ kcal mol⁻¹). The H-abstraction of the C14-H bond ($\Delta G^0 = 1.7$ – 4.8 kcal mol⁻¹) should be omitted due to the lower HOO[•] radical scavenging activity of C-H bonds compared with the N-H and O9-H bonds.^{17,51} However, in the aqueous solution, the SET reaction of the anion state should be considered.^{12,24,50}

Therefore, the total rate constant (k_{overall}) of GLD antiradical activity against the HOO[•] radical in the gas phase, pentyl ethanoate and water can be calculated using eqn (17) and (18). Table 3 and Fig. 3 show the final results.

Nonpolar environments:

$$k_{\text{overall}} = k_{\text{app}}(\text{FHT}(\text{O9-H})\text{-neutral}) + k_{\text{app}}(\text{FHT}(\text{N-H})\text{-neutral}) \quad (17)$$

Water at physiological pH:

$$k_{\text{overall}} = k_f(\text{SET-anion}) + k_f(\text{FHT}(\text{O9-H})\text{-neutral}) + k_f(\text{FHT}(\text{N-H})\text{-neutral}) \quad (18)$$

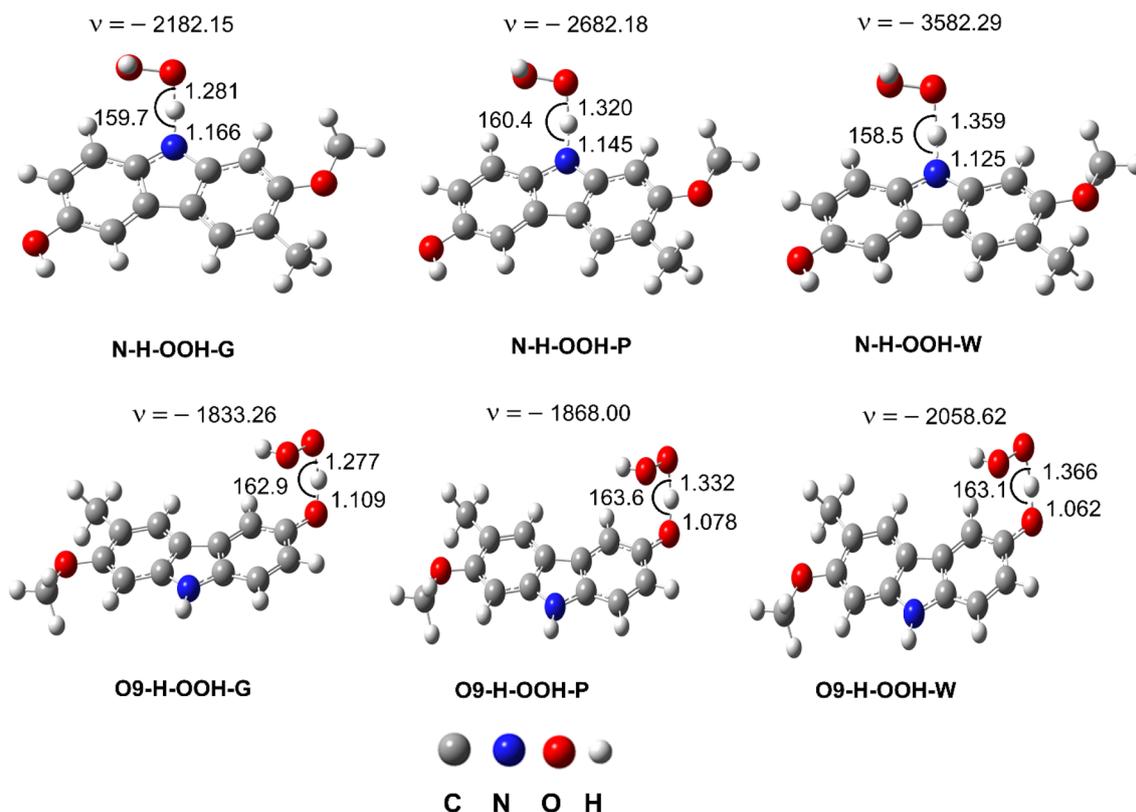


Fig. 3 The TS structures of the HOO[•] + GLD reaction following the FHT pathway; imaginary frequencies given in cm⁻¹, bond lengths in Å and bond angles in °.



Gas-phase kinetic computations revealed that the HOO[•] antiradical activity of **GLD** mainly proceeds *via* H-abstraction of the O9–H bond ($k_{(O9-H)} = 8.43 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, $I = 98.9\%$). The contribution of FHT reactions of the N–H bond was negligible ($I = 1.1\%$). This is in agreement with thermodynamic data (Table 1). Similar trend was also observed in the lipid medium, H-abstraction at the O9–H bond contributed 99.2% ($k_{(O9-H)} = 3.50 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$) to the overall rate constant ($k_{\text{overall}} = 3.53 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$), whereas, the contribution of the N–H bond was only 0.8% ($k_{(N-H)} = 2.90 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$) in the k_{overall} . In aqueous solution, SPLET was the predominant mechanism with $k_f = 7.90 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ ($\Delta G^\ddagger = 1.6 \text{ kcal mol}^{-1}$), however, the FHT reaction of the O9–H and N–H bond still contributed approximately 4.0% of the k_{overall} . Thus in the polar environment the HOO[•] antiradical activity of **GLD** is roughly 233 times faster than in the lipid environment ($k_{\text{overall}} = 8.23 \times 10^6$ vs. $3.53 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, respectively). Nevertheless, in the lipid environment the HOO[•] radical scavenging activity of **GLD** is still higher than that of typical antioxidants such as BHT ($k_{\text{overall}} = 1.70 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$),¹⁴ trolox ($k_{\text{overall}} = 3.40 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$),¹⁹ ascorbic acid ($k_{\text{overall}} = 5.71 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$),²⁰ or resveratrol ($k_{\text{overall}} = 1.31 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$).²⁴ In the polar environment, **GLD** is about 33 and 92 times more active than BHT ($k_{\text{overall}} = 2.51 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$),¹⁴ and trolox ($k = 8.96 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$),¹⁹ respectively, but less active than ascorbic acid ($k = 9.97 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$),²⁰ and resveratrol ($k = 5.62 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$).²⁴ Thus **GLD** is a promising radical scavenger in physiological environments.

3.3 The antiradical activity of **GLD** against ordinary free radicals in aqueous solution following the SET reaction

Although HOO[•] scavenging activity is a valuable comparative metric, the antiradical activity against different radicals often vary in a broad range. Therefore, the radical scavenging activity of **GLD** was subsequently modeled against a variety of common free radicals, including HOO[•], CH₃OO[•], CCl₃OO[•], HO[•], CH₃O[•], CCl₃O[•], NO, NO₂, O₂^{•-}, SO₄^{•-}, N₃[•], ABTS^{•+} and DPPH. The hydroperoxyl radical scavenging activity of **GLD** ($I = 96.0\%$) is determined by the SET mechanism. Consequently, in this

investigation, the antiradical activity against these radicals in water at pH = 7.4 was evaluated using the SET mechanism and the findings are shown in Table 4.

GLD should have high activity against CH₃O[•], CH₃OO[•], CCl₃OO[•], NO₂, SO₄^{•-}, DPPH and ABTS^{•+} radicals with $k_{\text{app}} \approx 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $k_f \approx 10^6 \text{ M}^{-1} \text{ s}^{-1}$, whereas NO, O₂^{•-}, HO[•], CCl₃O[•], and N₃[•] radicals cannot be eliminated by **GLD** under the studied conditions. By the SET reaction, **GLD** is less active against CCl₃O[•], and N₃[•] radicals than fraxin⁵⁵ or usnic acid,⁵⁶ but more effective against HOO[•] and CH₃OO[•] radicals. For HO[•], however, the prediction of low activity suggests that SET is not the correct mechanism; highly reactive radicals are known to follow alternative pathways (FHT or radical adduct formation to the neutral species) that for these radicals are essentially barrierless in aqueous media. Thus our results also highlight the limits of generalizations from one detailed study.⁵⁰

4. Conclusion

The antiradical activity of **GLD** against HOO[•], CH₃OO[•], CCl₃OO[•], HO[•], CH₃O[•], CCl₃O[•], NO, NO₂, O₂^{•-}, SO₄^{•-}, N₃[•], ABTS^{•+} and DPPH was studied using DFT calculations. In the physiological environments **GLD** exhibited significant antiradical activity. The overall rate constants for the antiradical trapping of **GLD** in water at pH = 7.40 and pentyl ethanoate were $k_{\text{overall}} = 8.23 \times 10^6$ and $3.53 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, respectively. The SPLET mechanism made contributions to the activity in water at pH 7.40, however, the FHT mechanism characterized the activity in nonpolar solvents. Additionally, it was found that **GLD** has strong antiradical activity against CH₃O[•], CH₃OO[•], CCl₃OO[•], NO₂, SO₄^{•-}, DPPH and ABTS^{•+} $k_{\text{app}} \approx 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $k_f \approx 10^6 \text{ M}^{-1} \text{ s}^{-1}$. According to the computed results, **GLD** is more effective at trapping HOO[•] than reference antioxidants like trolox and BHT in the physiological environment. The results suggest that **GLD** can join the long list of phytochemicals with good radical scavenging activity in physiological environments, emphasizing yet again the importance of varied plant sources in diets and in dietary supplements to maintain health and prevent disease.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research is funded by Funds for Science and Technology Development of the University of Danang under project number B2020-DN03-47 (M. V. B.).

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Table 4 Calculated kinetic data between **GLD**–O9–ANION (A⁻) and the selected radicals (ΔG^\ddagger , λ in kcal mol⁻¹; k_D , k_{app} and k_f in M⁻¹ s⁻¹)^a

Radicals	ΔG^\ddagger	λ	k_D	k_{app}	k_f
HO [•]	42.5	3.4	8.40×10^9	4.30×10^{-19}	4.30×10^{-22}
CH ₃ O [•]	2.1	4.5	7.90×10^9	7.60×10^9	7.60×10^6
CCl ₃ O [•]	24.1	21.2	7.50×10^9	1.30×10^{-5}	1.30×10^{-8}
HOO [•]	1.6	15.3	8.10×10^9	7.90×10^9	7.90×10^6
CH ₃ OO [•]	2.2	14.7	8.00×10^9	7.60×10^9	7.60×10^6
CCl ₃ OO [•]	1.4	16.8	7.60×10^9	7.50×10^9	7.50×10^6
NO	71.8	14.3	8.20×10^9	1.50×10^{-40}	1.50×10^{-43}
NO ₂	0.0	27.7	8.00×10^9	8.00×10^9	8.00×10^6
O ₂ ^{•-}	36.8	17.1	8.00×10^9	7.10×10^{-15}	7.10×10^{-18}
SO ₄ ^{•-}	14.1	17.6	7.70×10^9	2.90×10^2	2.90×10^{-1}
N ₃ [•]	52.3	2.4	7.90×10^9	3.00×10^{-26}	3.00×10^{-29}
DPPH	0.8	18.8	7.40×10^9	7.40×10^9	7.40×10^6
ABTS ^{•+}	0.0	11.8	7.40×10^9	7.40×10^9	7.40×10^6

^a $k_f = f \cdot k_{\text{app}}$; $f(A^-) = 0.001$.



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