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Oxoberberine: a promising natural antioxidant in physiological environments†

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Oxoberberine (**OB**, 2,10-dihydroxy-3,9-dimethoxy-8-oxo-protoberberine, artathomsonine), which was isolated from Artabotrys thomsonii, was shown to exhibit potent antioxidant activity *in vitro*, however that is the only reported evidence of the radical scavenging activity of this compound thus far. In the present study, thermodynamic and kinetic calculations were used to determine the free radical scavenging activity of **OB** against a range of biologically important species, under physiological conditions. In the first part the activity is calculated against the $HOO^{\bullet}$ radical that is both biologically important and a reference radical for comparison. It was found that **OB** has high antiradical capacity against $HOO^{\bullet}$ in both lipid medium and water at physiological pH with $k_{overall} = 1.33 \times 10^5$ and 1.73×10^6 M^{-1} s^{-1}, respectively. The formal hydrogen transfer mechanism defined the activity in nonpolar environments, whereas in the aqueous solution the single electron transfer competes with the hydrogen transfer pathway. The results showed that, in lipid medium, the $HOO^{\bullet}$ trapping capability of **OB** is better than typical antioxidants such as Trolox, BHT, resveratrol and ascorbic acid. Similarly, the activity of **OB** in water at pH 7.4 is roughly 19 and 7 times faster than those of Trolox and BHT, respectively, but slightly lower than the activities of resveratrol or ascorbic acid. In the second part, it was found that **OB** also exhibits high activity against other typical free radicals such as $CH_3O^{\bullet}$, $CH_3OO^{\bullet}$, $CCl_3OO^{\bullet}$, NO_2, $SO_4^{\bullet-}$, DPPH and $ABTS^{\bullet+}$ with k_f ranging from 2.03×10^5 to 5.74×10^7 M^{-1} s^{-1}. Hence, it is concluded that **OB** is a promising radical scavenger in the physiological environment.

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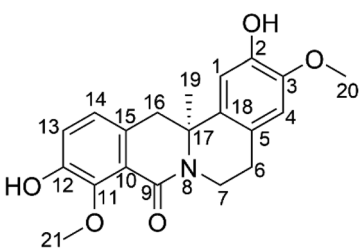
1. Introduction

The custard-apple family Annonaceae (Juss.) includes the genus *Artabotrys*, which is one of the largest genera.[1] The genus *Artabotrys* contains traditional medicinal plants used for the treatment of a variety of diseases, including malaria, scrofula, cholera, diabetes, stomach pain, asthma, and cough.[2–4] The search for the key active ingredients yielded oxoberberine (**OB**, 2,10-dihydroxy-3,9-dimethoxy-8-oxo-protoberberine, artathomsonine, Fig. 1), which was isolated from *Artabotrys thomsonii*.[1] This compound belongs to the berberine family, which has recently attracted attention due to its confirmed biological activities, including antidiabetic,[5] anticancer,[6,7] antimicrobial,[8,9] and antioxidant properties.[10] The latter is based on the berberine structure with two phenolic groups (Fig. 1) that would normally impose antioxidant properties on natural products. **OB** exhibited good antioxidant activity in the ferric reduction ability potential (FRAP) assay with 0.2 ± 0.05 μg gallic acid equivalents per mg compound,[1] but this is the only evidence thus far for its antioxidant activity.

Oxidative stress (OS) is a chemical term that refers to an imbalance in the synthesis and consumption of oxidants in biological systems.[11] Despite the presence of oxidants of various chemical natures in such systems, free radicals (FR) stand out in the OS environment. They are highly reactive and have the



Oxoberberine (OB)

Fig. 1 Chemical structure of oxoberberine (**OB**).

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ability to initiate chain reactions, leading to spreading molecular damage.[12] There are several different types of FR, the majority of which can be divided into two categories: reactive oxygen species (ROS, *i.e.* $HO^{\bullet}$, $CH_3O^{\bullet}$, $HOO^{\bullet}$, $CH_3OO^{\bullet}$, $O_2^{\bullet-}$, $SO_4^{\bullet-}$) and reactive nitrogen species (RNS, *i.e.* NO, NO_2, $N_3^{\bullet}$). The hydroxyl radical has been blamed for the majority of ionizing radiation-induced DNA oxidation and tissue damage,[13–15] whereas peroxynitrite is a potent oxidant and a very toxic species that can damage lipids, proteins, and DNA when it reacts with $O_2^{\bullet-}$.[16,17] The $HOO^{\bullet}$ radical is considered a model free radical to evaluate the antiradical activity of organic compound due to its moderate reactivity,[12,18] while studies on the radical scavenging activity against other typical ROS and RNS such as $HO^{\bullet}$, $CH_3O^{\bullet}$, $CCl_3O^{\bullet}$, $HOO^{\bullet}$, $CH_3OO^{\bullet}$, $CCl_3OO^{\bullet}$, NO, NO_2, $O_2^{\bullet-}$, $SO_4^{\bullet-}$ and $N_3^{\bullet}$ are crucial to provide practical information about the antioxidant activity of natural products.[19,20]

The benefit of computational approaches to the analysis of structure–activity relationship has been demonstrated in a number of previous studies, making it a valuable addition to the medicinal chemistry toolbox.[12,21–27] In this study, we used computational methods to analyze the radical scavenging activity of **OB** in physiological environments against $HO^{\bullet}$, $CH_3O^{\bullet}$, $CCl_3O^{\bullet}$, $HOO^{\bullet}$, $CH_3OO^{\bullet}$, $CCl_3OO^{\bullet}$, NO, NO_2, $O_2^{\bullet-}$, $SO_4^{\bullet-}$, $N_3^{\bullet}$, DPPH and $ABTS^{\bullet+}$.

2. Computational details

The Gaussian 09 suite of programs[28] was used to perform all calculations in this study by using the density functional theory (DFT) approach. All computations were performed using the M06-2X functional and the 6-311++G(d,p) basis set.[29] The M06-2X functional is one of the most dependable approaches for studying radical reaction thermodynamics and kinetics.[30,31] With only modest inaccuracies when compared to experimental data (k_{calc}/k_{exp} ratio = 1–2.9),[18,32–35] and widely applied to evaluate the radical scavenging activity of both natural and artificial compounds.[36–39] The SMD technique,[36] which is often employed when modelling the radical scavenging activity of antioxidants,[30,35,37] was utilized to predict the solvent effects of water and pentyl ethanoate.

The kinetic calculations were performed using the quantum mechanics-based test for overall free radical scavenging activity (QM-ORSA) protocol.[18] Standard transition state theory (TST) and a 1 M standard state at 298.15 K were used to compute the rate constants (k).[35,38–44] More details on the method can be found in Table S1, ESI.†

3. Results and discussion

3.1. Conformer evaluation

The OH and OMe groups in **OB** can rotate around the single bonds to generate a variety of conformers, according to research on the **OB** structure. Thus, the probable **OB** conformers were screened[45] in the first stage, and the five lowest electronic energy conformers were then examined using the M06-2X/6-311++G(d,p) level of theory (Fig. 2). Among the conformers, **OB** has the lowest Gibbs free energy value while OB1–OB4 have higher free energy of formation than **OB** by 2.3–5.2 kcal mol^{-1}. When the relative populations of the conformers were estimated using the Maxwell–Boltzmann distribution,[46,47] it was found that **OB** is dominant (>97%), hence this conformer was studied in the followings.

3.2. The HOO radical scavenging activity of OB

3.2.1. The thermodynamic study. Thermodynamic calculations based on the three common radical scavenging mechanisms were used to assess antioxidant activity. These are (i) formal hydrogen transfer (FHT), (ii) single electron transfer-proton transfer (SETPT), and (iii) sequential proton-loss

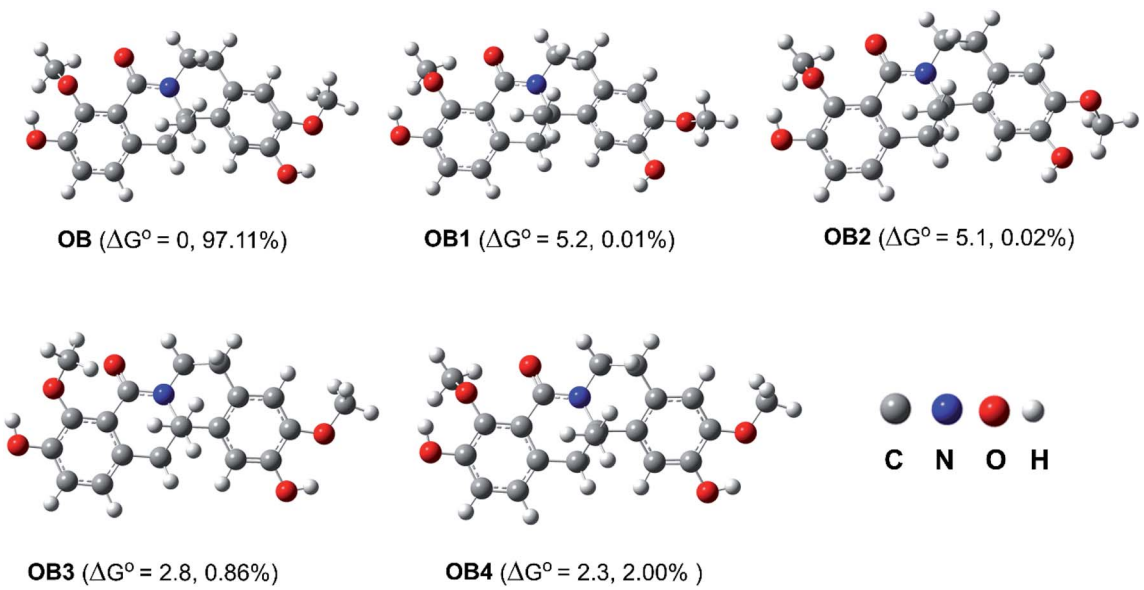

Fig. 2 The main conformers of OB (ΔG° (in kcal mol^{-1}) compared with OB).

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Table 1 The computed thermodynamic parameters (BDE, PA, IE in kcal mol^{-1}) of **OB** and ΔG^{o} (kcal mol^{-1}) of the first step of the HOO$^{\bullet}$ + **OB** reaction in the studied solvents

	Pentyl ethanoate						Water					
Positions	BDE	ΔG^{o}	PA	ΔG^{o}	IE	ΔG^{o}	BDE	ΔG^{o}	PA	ΔG^{o}	IE	ΔG^{o}
C6–H	88.4	1.5			132.0	69.3	88.9	1.2			107.0	26.3
C7–H	92.8	6.4					94.2	4.5				
C16–H	88.9	2.4					89.8	1.1				
O2–H	86.5	0.2	87.4	106.5			88.0	−1.6	48.2	56.5		
O12–H	87.2	0.2	86.4	105.3			87.7	−2.6	44.9	52.8		

electron transfer (SPLET).[48] The HOO$^{\bullet}$ radical quenching of **OB** in physiological environments (pentyl ethanoate for a lipid medium and water at pH 7.4) was examined first by calculating the thermodynamic parameters (bond dissociation enthalpy (BDE), ionization energy (IE), proton affinity (PA) and the Gibbs free energy change (ΔG^{o}) of the first step of each mechanism) for all bonds. Table 1 summarizes the findings.

It was found that BDE values in the lipid medium range from 86.5 to 92.8 kcal mol^{-1}, which are 0.5–1.5 kcal mol^{-1} lower than those in the aqueous solution. The IE values are larger than the BDEs in all of the studied solvents. This suggests that the single electron transfer (SET) pathway is not feasible in either of the environments. However, the deprotonation at the O2(12)–H bond could preferentially occur in water due to lower PA values compared with the BDEs and IEs (PA = 44.9–48.2 kcal mol^{-1}).

The **OB** + HOO^{-} reaction was only spontaneous in the thermodynamic sense following the hydrogen transfer pathway, particularly at the O2(12)–H bonds (ΔG^{o} = −2.6 to 0.2 kcal mol^{-1}). In polar media such as water at pH = 7.40, the deprotonation and stable states of **OB** should also be considered.

3.2.2. The kinetic study. The protonation state of **OB** at physiological pH must be assessed in order to evaluate the feasibility and kinetics of electron transfer processes from the deprotonated species. The **OB** structure allows protonation at the N8 site (1), as well as deprotonation of the alcohol molecule at the O12–H position (2). Following the literature, the pK_a values of **OB** were computed based on the model reactions (1) and (2), the results are presented in Fig. 3.[49,50]

$$R_2NH^{+} \leftrightarrows R_2N + H^{+} \quad (1)$$

$$ROH \leftrightarrows RO^{-} + H^{+} \quad (2)$$

The computed pK_a values for the amine were <1, while the O12–H group had a pK_a of 9.57. As a consequence, the cationic state is not relevant but there is still a non-negligible proportion of the mono-anionic state (O12–H, 0.7%) in a pH 7.4 aqueous solution (Fig. 3). Thus, both the neutral and anionic states were considered in the kinetic evaluation of HOO$^{\bullet}$ antiradical activity of **OB** in water at pH of 7.4. eqn (3) and (4) can be used to assess

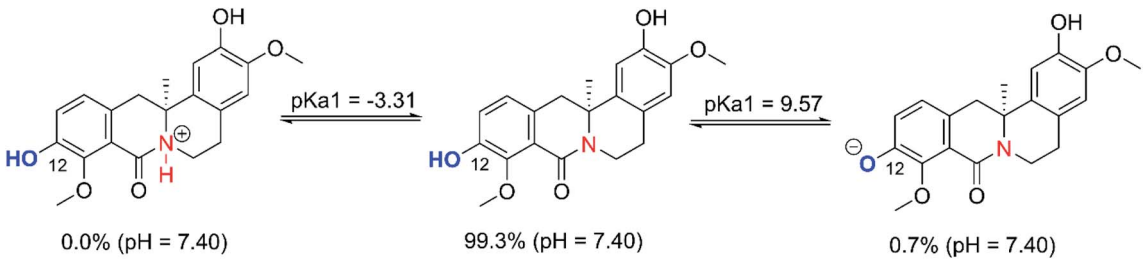

Fig. 3 Possible protonation states of **OB** at pH = 7.40.

Table 2 Computed $\Delta G^{\ddagger}$ in kcal mol^{-1}, tunneling correction (κ), Γ in %, and k_{app}, k_f, and $k_{overall}$ in M^{-1} s^{-1} of **OB** + HOO$^{\bullet}$ reactions[a]

		Pentyl ethanoate				Water					
Mechanisms		$\Delta G^{\ddagger}$	κ	k_{app}	Γ	$\Delta G^{\ddagger}$	κ	k_{app}	f	k_f	Γ
SET						6.2	15.7	1.80×10^{8}	0.007	1.26×10^{6}	73.0
FHT	O2–H	17.3	2459.8	3.30×10^{3}	2.5	15.5	7917.2	2.00×10^{5}	0.993	1.99×10^{5}	11.5
	O12–H	16.2	15 234	1.30×10^{5}	97.5	17.3	199 934	2.70×10^{5}	0.993	2.68×10^{5}	15.5
$k_{overall}$				1.33×10^{5}						1.73×10^{6}	

[a] $k_f = f.\ k_{app}$; $\Gamma = k.100/k_{overall}$; the nuclear reorganization energy (λ, in kcal mol^{-1}).

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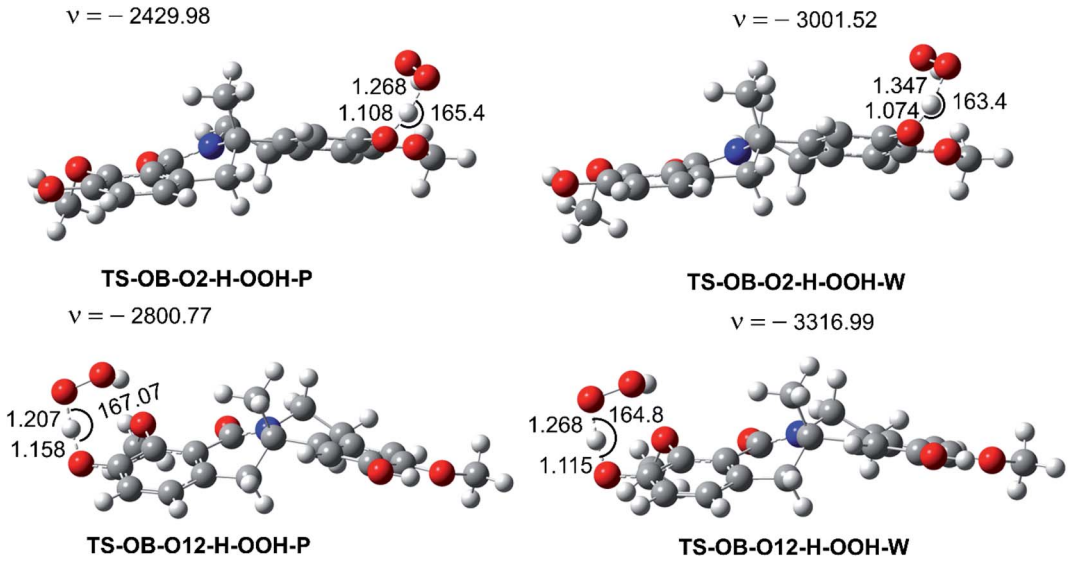

Fig. 4 The selected TS structures of the HOO˙ + **OB** reaction following the FHT pathway (P: pentyl ethanoate, W: water).

the total rate constant ($k_{overall}$) of **OB**'s antiradical behavior against HOO˙ radical in the physiological environments. The results are presented in Table 2 and Fig. 4.

Lipid environment:

$$k_{overall} = k_{app}(\text{FHT(O2–H)-neutral}) + k_{app}(\text{FHT(O12–H)-neutral}) \quad (3)$$

Water at physiological pH:

$$k_{overall} = k_f(\text{SET-anion}) + k_f(\text{FHT(O2–H)-neutral}) + k_f(\text{FHT(O12–H)-neutral}) \quad (4)$$

In lipid media, the H-abstraction of the O12–H bond dominates in the HOO˙ radical scavenging of **OB** with a rate constant of $k = 1.30 \times 10^5\ M^{-1}\ s^{-1}$, whereas in aqueous solution, SPLET was the main mechanism with $k = 1.26 \times 10^6\ M^{-1}\ s^{-1}$ ($\Delta G^{\ddagger} = 6.2$ kcal mol^{-1}, $\Delta G^{o} = 4.0$ kcal mol^{-1}). The FHT reaction of the O2–H bond contributes about 11.5% of the overall rate constant in the aqueous solution, and only = 2.5% ($k = 3.30 \times 10^3\ M^{-1}\ s^{-1}$) in the lipid medium. Overall the HOO˙ antiradical activity of **OB** in the polar environment is approximately 13 times faster than in the lipid medium ($k_{overall} = 1.73 \times 10^6\ M^{-1}\ s^{-1}$ *vs.* $k_{overall} = 1.33 \times 10^5\ M^{-1}\ s^{-1}$, respectively).

Therefore, in lipid medium, the HOO˙ trapping capability of **OB** is higher than that of typical antioxidants such as Trolox ($k_{overall} = 3.40 \times 10^3\ M^{-1}\ s^{-1}$),[33] BHT ($k_{overall} = 1.70 \times 10^4\ M^{-1}\ s^{-1}$),[51] resveratrol ($k_{overall} = 1.31 \times 10^4\ M^{-1}\ s^{-1}$)[37] and ascorbic acid ($k_{overall} = 5.71 \times 10^3\ M^{-1}\ s^{-1}$).[18] In water at physiological pH, **OB** is about 13 and 7 times more active than Trolox ($k = 8.96 \times 10^4\ M^{-1}\ s^{-1}$)[33] and BHT ($k_{overall} = 2.51 \times 10^5\ M^{-1}\ s^{-1}$),[51] respectively, but slightly less active than resveratrol ($k = 5.62 \times 10^7\ M^{-1}\ s^{-1}$),[37] ascorbic acid ($k = 9.97 \times 10^7\ M^{-1}\ s^{-1}$),[18] cannabidiolic acid ($k = 2.40 \times 10^6\ M^{-1}\ s^{-1}$),[52] or carnosic acid ($k = 4.73 \times 10^6\ M^{-1}\ s^{-1}$).[53] Hence, **OB** is a promising radical scavenger in physiological environments.

3.3. The antiradical activity of OB against ordinary free radicals in aqueous solution

Whereas HOO˙ scavenging activity is useful measure for comparison, there are variances in radical scavenging activities against different radical species. Therefor next the antiradical activity of **OB** was modeled against a range of common free radicals such as HO˙, $CH_3O^{\bullet}$, $CCl_3O^{\bullet}$, HOO˙, $CH_3OO^{\bullet}$, $CCl_3OO^{\bullet}$, NO, NO_2, $O_2^{\bullet-}$, $SO_4^{\bullet-}$, $N_3^{\bullet}$, DPPH and $ABTS^{\bullet+}$ that are used in experimental antiradical assays. The antiradical activity of **OB** against these free radicals may follow either of the typical mechanisms such as FHT, SETPT, SPLET[48] or/and radical adduct formation (RAF),[12] however, the study showed that the SET mechanism plays a determining role in the hydroperoxyl radical scavenging activity of **OB** ($I = 73.0\%$). Thus in order to rationalize computing time and for comparability with previous data,[19,20] the interaction of the anion state with these radicals was examined following the principal aqueous phase

Table 3 Calculated kinetic data between OB-O12-ANION and the selected radicals

Radical	$\Delta G^{\ddagger}$	λ	k_{app}	k_f[a]
HO˙	13.5	3.8	7.90×10^2	5.53
$CH_3O^{\bullet}$	0.7	4.9	8.20×10^9	5.74×10^7
$CCl_3O^{\bullet}$	14.6	21.6	1.20×10^2	8.40×10^{-1}
HOO˙	6.2	15.7	1.80×10^8	1.26×10^6
$CH_3OO^{\bullet}$	7.3	15.1	2.90×10^7	2.03×10^5
$CCl_3OO^{\bullet}$	0.0	17.2	6.90×10^9	4.83×10^7
NO	92.6	14.7	8.40×10^{-56}	5.88×10^{-58}
NO_2	1.1	28.1	8.20×10^9	5.74×10^7
$O_2^{\bullet-}$	51.1	17.5	2.00×10^{-25}	1.40×10^{-27}
$SO_4^{\bullet-}$	6.6	18.0	8.90×10^7	6.23×10^5
$N_3^{\bullet}$	14.7	2.8	1.00×10^2	7.00×10^{-1}
DPPH	4.1	19.2	3.50×10^9	2.45×10^7
$ABTS^{\bullet+}$	1.6	12.2	6.60×10^9	4.62×10^7

[a] $k_f = f.\ k_{app}$; $f(A^-) = 0.007$.

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mechanism (the SET reaction) at pH = 7.4, with the results presented in Table 3.

According to the calculations, **OB** should have high activity against $CH_3O^{\bullet}$, $CH_3OO^{\bullet}$, $CCl_3OO^{\bullet}$, NO_2, $SO_4^{\bullet-}$ radicals with k_f ranging from 2.03×10^5 to 5.74×10^7 M^{-1} s^{-1}, whereas $HO^{\bullet}$, $CCl_3O^{\bullet}$, NO, $O_2^{\bullet-}$ and $N_3^{\bullet}$ radicals could not be removed under the examined conditions. The results also suggest that **OB** can exhibit the significant DPPH and $ABTS^{\bullet+}$ radicals scavenging activity ($k_f = 2.45 \times 10^7$ and 4.62×10^7 M^{-1} s^{-1}, respectively) in water at pH = 7.40. Compared with fraxin[19] and usnic acid,[20] **OB** exhibited the lower $HO^{\bullet}$, $CCl_3O^{\bullet}$, $N_3^{\bullet}$ antiradical activity than that of these compounds by the SET reaction, whereas the opposite trend was observed at peroxyl radicals *i.e.* $HOO^{\bullet}$, and $CH_3OO^{\bullet}$.

4. Conclusion

Computer calculations were used to evaluate the radical scavenging capacity of oxoberberine against $HO^{\bullet}$, $CH_3O^{\bullet}$, $CCl_3O^{\bullet}$, $HOO^{\bullet}$, $CH_3OO^{\bullet}$, $CCl_3OO^{\bullet}$, NO, NO_2, $O_2^{\bullet-}$, $SO_4^{\bullet-}$, $N_3^{\bullet}$, DPPH and $ABTS^{\bullet+}$. In the physiological environment **OB** exhibited high antiradical capacity. Concerning the reference system $HOO^{\bullet}$, the overall rate constant of the radical scavenging of **OB** was 1.73×10^6 and 1.33×10^5 M^{-1} s^{-1} in the aqueous solution and lipid medium, respectively. The FHT mechanism defined the activity in nonpolar solvents, whereas that for water at pH = 7.40 had contributions from the SPLET as well as FHT pathways. It was also found that **OB** exhibits high antiradical activity against $CH_3O^{\bullet}$, $CH_3OO^{\bullet}$, $CCl_3OO^{\bullet}$, NO_2, $SO_4^{\bullet-}$, DPPH and $ABTS^{\bullet+}$ with k_f ranging from 2.03×10^5 to 5.74×10^7 M^{-1} s^{-1}. The calculated results showed that the $HOO^{\bullet}$ trapping capability of **OB** is also higher than those of typical antioxidants such as Trolox and BHT in both the lipid and polar environments.

Conflicts of interest

There are no conflicts to declare.

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