Antioxidant Activity of Natural Samwirin A: Theoretical and Experimental Insights

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ABSTRACT: Samwirin A (SW), a natural compound isolated from Sambucus williamsii or Rourea harmandiana, is known to exhibit potent antiosteoporosis activity and promote cell proliferation in rat osteoblast-like UMR 106 cells. Antiosteoporosis activity suggests that the compound must also exhibit antioxidant activity but this has not been studied thus far. In the present study, the antioxidant activity of SW was examined by experimental and computational studies. It was found that SW exhibits good hydroperoxyl scavenging activity, particularly in water at physiological pH ($k_{\text{overall}} = 1.01 \times 10^7 \text{ M}^{-1} \text{s}^{-1}$). The single-electron transfer mechanism defines the HOO• + SW reaction in water, while the activity in the lipid medium is moderate and it follows the formal hydrogen transfer mechanism. The rate constant of the HOO• scavenging reaction in the aqueous solution is about 78 times higher than the reference compound Trolox. The computational results are in line with experimental data underscoring that SW is a promising radical scavenger in aqueous media at physiological pH.

1. INTRODUCTION

Samwirin A (SW, Figure 1) is a rare neolignan compound isolated from the stems and branches of Sambucus williamsii1 and Cichorium glandulosum roots, respectively.2 SW showed antiosteoporosis activity, significantly promoting cell proliferation on rat osteoblast-like UMR 106 cells.1 Recently, we have identified SW in stems of Rourea harmandiana (Table S2, Supporting Information), a plant that was used as a traditional drug to treat bone fractures.3

Oxidative stress is one of the primary factors contributing to the pathogenesis of osteoporosis.4 Clinical studies demonstrated that increased oxidative stress shows a significant correlation with decreased bone mineral density. In osteoporotic women, the blood level of antioxidants was low, and supplementing antioxidants led to a measurable increase in bone mineral density.5,6 In vitro studies also showed that the presence of reactive oxygen species (ROS) increases osteoclast activity and reduces osteoblast metabolisms. The oxidative stress-induced inhibition of osteoblast metabolisms can be prevented by treatment with antioxidants.6 Several natural compounds show antiosteoporosis activity attributed to their antioxidant capacities.7,8 As mentioned above, SW has demonstrated an antiosteoporosis effect; furthermore, SW contains two phenolic groups in its structure (Figure 1), which
is a good indicator of antioxidant activity, yet the antioxidant properties of SW have not been studied thus far.

Previous studies have shown that quantum chemistry offers a convenient avenue for studying the structure–activity relationship in bioactive molecules, informing drug development efforts with potential activity motifs.\(^{25,27}\) Consistently, the combination of theoretical and experimental studies can evaluate the antioxidant activity of natural products effectively and accurately.\(^{18-20}\) Thus, in this work, the antioxidant activity of SW from *R. harmandiana* was investigated by both computational and experimental methods.

### 2. RESULTS AND DISCUSSION

#### 2.1. ABTS Antioxidant Assay.

To initial evaluate the antioxidant activity of SW, the ABTS assay was performed following the literature,\(^{21}\) using Trolox as a reference antioxidant. It was found that SW is only capable of substantially lower ABTS*• scavenging activity (IC\(_{50}\) = 74.27 ± 5.94 μM) than Trolox (IC\(_{50}\) = 25.16 ± 1.64 μM) under the studied conditions. To correctly interpret this result, one has to consider that ABTS assay is performed in an organic solvent, and thus the result indicates that the radical scavenging activity of SW in organic solvents is lower than that of Trolox. However, this activity in water, particularly at physiological pH, might be improved due to the deprotonation of phenolic groups,\(^{7,22}\) (O5−H and O4′−H), and this needs further investigation by quantum chemical calculations.

#### 2.2. HOO• Radical Scavenging Activity of SW.

##### 2.2.1. Gas-Phase Evaluation.

In the absence of any double bonds in the chemical structure, the antioxidant activity of a phenolic compound can occur according to either of the three typical mechanisms: sequential proton-loss electron transfer (SPLET), formal hydrogen transfer (FHT), and single-electron transfer proton transfer (SETPT).\(^{23,24}\) Thus, in the first step, key thermodynamic parameters of SW were calculated: proton affinity (PA), bond dissociation enthalpy (BDE), and ionization energy (IE), which characterize the propensity of the compound to react via the SPLET, FHT, and SETPT pathways, respectively. These parameters were first calculated in the gas phase at the M06-2X/6-311++G(d,p) level of theory (Table 1).\(^{22,25}\)

| Positions | BDE (kcal mol\(^{-1}\)) | ΔG\(_{\text{PA}}\) (kcal mol\(^{-1}\)) | ΔG\(_{\text{IE}}\) (kcal mol\(^{-1}\)) | ΔG\(_{\text{SETPT}}\) (kcal mol\(^{-1}\)) |
|-----------|-------------------------|----------------------------------|---------------------------------|----------------------------------|
| C2−H      | 83.4                    | −2.1                             | 165.1                           | 142.6                            |
| C3−H      | 85.8                    | −1.0                             |                                 |                                  |
| O5−H      | 82.5                    | −3.7                             | 342.4                           | 190.5                            |
| O4′−H     | 87.2                    | 1.2                              | 341.7                           | 189.3                            |

The lowest BDE value was predicted for O5−H at 82.5 kcal mol\(^{-1}\). This value is still higher than the lowest BDEs of resveratrol (83.9 kcal mol\(^{-1}\)),\(^{25}\) piceatannol (73.1 kcal mol\(^{-1}\)) or 75.1 kcal mol\(^{-1}\), Trolox (73.0 kcal mol\(^{-1}\)),\(^{26}\) or ascorbic acid (73.9 kcal mol\(^{-1}\)).\(^{29}\) The BDE values of the C2(3)−H bonds are 83.4 and 85.8 kcal mol\(^{-1}\), respectively, while that of the O5−H is lower than the O4′−H bond by about 4.7 kcal mol\(^{-1}\). The PA values for O5(4′)−H bonds (PA = 342.4 and 341.7 kcal mol\(^{-1}\), respectively) are significantly higher than the related BDEs. At the same time, the ionization of SW is more difficult than the bond dissociation, as shown by the higher IE value (IE = 165.1 kcal mol\(^{-1}\)). The data (Table S3, Supporting Information) show that the lowest BDE was obtained at the O5−H bond (BDE(O5−H) = 80.6–82.1 kcal mol\(^{-1}\)) in all of the studied solvents and it is lower than the IE values by about 19.3–42.6 kcal mol\(^{-1}\). Consistently, the antioxidant activity of SW in the gas phase and organic solvents is expected to favor the FHT pathway.

To confirm the preferred antioxidant pathway, the Gibbs free-energy changes of the first steps of the SW + HOO• reactions were also calculated following each of the pathways (Table 1). The HOO• + SW reactions are only spontaneous for FHT (ΔG\(_{\text{FHT}}\) = −3.7 to 1.2 kcal mol\(^{-1}\)), whereas the other reactions are not spontaneous with high positive Gibbs free-energy change values (ΔG\(_{\text{G}}\)(SP) = 189.3–190.5 kcal mol\(^{-1}\) and ΔG\(_{\text{G}}\)(SET) = 142.6 kcal mol\(^{-1}\)). Thus, the calculated data suggest that the SW + HOO• reaction in the gas phase can only follow the FHT reaction, and this pathway should be investigated in the kinetic study.

The kinetics of the SW + HOO• reaction was computed following the FHT pathway using the quantum mechanics-based test for the overall free-radical scavenging activity (QM-ORSA) protocol (Table 2 and Figure 2).\(^{30,31}\) The study showed that the HOO• quenching of SW was defined by the hydrogen transfer of the O5−H bond with ΔG\(_{\text{G}}\) = 12.0 kcal mol\(^{-1}\), k\(_{\text{f}}\) = 6.63 × 10\(^8\) M\(^{-1}\) s\(^{-1}\), T = 98.1%, while the radical trapping of the other reactions makes only minor contributions with T = 0.2–1.1%. The tunneling corrections (calculated using the Eckart barrier) closely correlated with the rate constants of the HOO• scavenging activity. Tunneling corrections are introduced to account for the ability of the hydrogen atoms to tunnel through the potential barrier in reactions involving hydrogen abstraction, hence the correlation is expected but not always observed; here, it confirms the suitability of the FHT model. The overall rate constant of the SW + HOO• reaction is k\(_{\text{overall}}\) = 6.75 × 10\(^5\) M\(^{-1}\) s\(^{-1}\), which is around 27.7 times lower than that of Trolox (k = 1.87 × 10\(^7\) M\(^{-1}\) s\(^{-1}\)).\(^{22}\)

#### 2.2.2. Antiradical Activity of SW in Solvents.

Previous studies confirmed that the protonation state could strongly influence the HOO• radical scavenging activity of phenolic compounds.\(^{25,31,34}\) Thus, in this section, the proton dissociation equilibria of SW were first considered. As it was found in the thermodynamic study, the lowest PA value in the gas phase was of the O4′−H bond. The calculations for a water medium (Table S3, Supporting Information) showed that the deprotonation can occur in two steps: at O4′−H (PA = 45.4 kcal mol\(^{-1}\)) and O5−H (PA = 46.6 kcal mol\(^{-1}\)) bonds, respectively. Therefore, the k\(_{\text{f}}\) values were calculated for these bonds following previous studies (Figure 3).\(^{25,35}\) The

### Table 2. Computed ΔH, ΔG\(_{\text{G}}\) in kcal mol\(^{-1}\), Tunneling Corrections (κ), k\(_{\text{f}}\) (M\(^{-1}\) s\(^{-1}\)), and Branching Ratios (Γ, %) for the HOO• + SW Reactions

| Positions | ΔH (kcal mol\(^{-1}\)) | ΔG\(_{\text{G}}\) (kcal mol\(^{-1}\)) | κ | k\(_{\text{f}}\) (M\(^{-1}\) s\(^{-1}\)) | Γ (%) |
|-----------|------------------------|-------------------------------|---|-----------------|--------|
| C2−H      | 5.8                    | 16.5                          | 710.1 | 3.85 × 10\(^3\) | 0.6    |
| C3−H      | 6.2                    | 16.3                          | 221.4 | 1.57 × 10\(^3\) | 0.2    |
| O5−H      | 2.3                    | 12.0                          | 62.1  | 6.63 × 10\(^8\) | 98.1   |
| O4′−H     | 7.3                    | 16.6                          | 1625.9| 7.23 × 10\(^3\) | 1.1    |
| k\(_{\text{overall}}\) | 6.75 × 10\(^5\) | | | | |
calculated $pK_{a1}$ and $pK_{a2}$ were 9.71 and 10.22, respectively. Based on the calculated $pK_a$ values, in the aqueous solution at pH = 7.40, SW exists predominantly in two states: neutral (HA, 99.5%) and anionic ($A^-$, 0.5%), whereas the neutral state (HA) is the main form of SW in the lipid medium. Thus, the kinetics of the SW + HOO• reaction in the physiological environments were computed following the QM-ORSA protocol, using the solvation model based on the quantum mechanical charge density of a solute molecule interacting with a continuum (SMD) to account for the role of the solvent. This approach to model the role of media on radical reactions has been verified in previous works. Since in previous works, pentyl ethanoate and water were used to model the physiological environments to account for the conditions of the ABTS assay, here, DMSO was also modeled for comparison. The overall rate constants $k_{overall}$ were determined following reactions 1 and 2, and the results are presented in Table 3.

In water at physiological pH

$$k_{overall} = k_f(O5-H(neutral)) + k_f(SET - anion)$$

(1)

In aprotic media

$$k_{overall} = k_{app}(O5-H)$$

(2)

As shown in Table 3, the rate constant of the HOO• + SW reaction in pentyl ethanoate and DMSO are moderate with the overall rate constants $k_{overall} = 5.20 \times 10^4$ and $6.70 \times 10^3$ M$^{-1}$ s$^{-1}$, respectively. Thus, as shown in the gas-phase results, SW exhibits lower HOO• radical scavenging activity than Trolox.

Figure 2. Optimized structures of transition states (TS) along the FHT mechanism of the SW + HOO• reaction in different media (W: water; G: gas phase; D: dimethyl sulfoxide (DMSO); and P: pentyl ethanoate).

Figure 3. Acid dissociation equilibria of SW at pH = 7.40.
Table 3. Computed $\Delta G^\circ$ (kcal mol$^{-1}$), $\kappa$, $k_{app}$, $k_{overall}$ (M$^{-1}$ s$^{-1}$), Molar Fractions ($f$), and $\Gamma$ at 298.15 K for the SW + HOO$^*$ Reaction in the Studied Media$^a$

| solvents            | mechanisms | $\Delta G^\circ$ | $\kappa$ | $k_{app}$ | $f$   | $k_i$ | $\Gamma$   | $k_{Tolon}$ |
|---------------------|------------|------------------|----------|-----------|-------|-------|-------------|-------------|
| pentyl ethanoate    | FHT        | 14.6             | 389.7    | 5.20 $\times$ 10$^4$ | 0.005 | 1.00 $\times$ 10$^6$ | 100.0       | 1.00 $\times$ 10$^{-16}$ |
| DMSO                | FHT        | 16.1             | 688.5    | 6.70 $\times$ 10$^3$ | 0.120 | 1.91 $\times$ 10$^2$ | 98.8        | 1.20 $\times$ 10$^{-4}$ |
| water               | SET        | 4.6              | 16.6$^a$ | 2.00 $\times$ 10$^3$ | 0.995 | 1.91 $\times$ 10$^2$ | 1.2         | 1.01 $\times$ 10$^{-16}$ |
|                     | FHT        | 15.7             | 6108.9   | 1.20 $\times$ 10$^5$ | 0.020 | 1.00 $\times$ 10$^6$ | 1.30 $\times$ 10$^{-16}$ |

$^a$Nuclear reorganization energy ($\lambda$, kcal mol$^{-1}$). $^b$Ref 22. $f = \%A^\circ$/100; $k_i = k_{app}$; $\Gamma = k_j \times 100/k_{overall}$.

$(k_{overall}(\text{pentyl ethanoate}) = 1.00 \times 10^6$ M$^{-1}$ s$^{-1}$,$^2$ $k_{overall}(\text{DMSO}) = 1.20 \times 10^4$ M$^{-1}$ s$^{-1}$) in organic solvents. This is in line with the experimental data from the ABTS assay and confirms that the antiradical activity of SW is lower than that of Trolox in DMSO. The rate constant of the HOO$^*$ + SW-O$S$–H reaction also makes a small contribution with a rate constant of $k_j = 1.19 \times 10^5$ M$^{-1}$ s$^{-1}$; however, this reaction only contributes $\sim$1.2% of the overall antiradical activity. In contrast, the SW shows good HOO$^*$ scavenging activity in water at physiological pH with $k_{overall} = 1.01 \times 10^9$ M$^{-1}$ s$^{-1}$, which is about 78 times faster than that of Trolox ($k = 1.30 \times 10^9$ M$^{-1}$ s$^{-1}$).$^{22}$ Comparison with some natural products indicated that the HOO$^*$ radical trapping activity of SW in water at physiological pH is fairly similar to ascorbic acid ($k = 9.97 \times 10^9$ M$^{-1}$ s$^{-1}$),$^{32}$ resveratrol ($k = 5.62 \times 10^9$ M$^{-1}$ s$^{-1}$),$^{33}$ higenamine ($k = 1.23 \times 10^9$ M$^{-1}$ s$^{-1}$),$^{38}$ or daphnetin ($k = 1.51 \times 10^9$ M$^{-1}$ s$^{-1}$).$^{40}$ Thus, SW is a promising antioxidant in water at physiological pH.

3. CONCLUSIONS

The antioxidant activity of phenolic compound samwirin A (SW) from R. harmandiana was successfully investigated. Calculations suggest that SW can exhibit moderate antiradical activity in nonpolar media ($k = 6.75 \times 10^4$ M$^{-1}$ s$^{-1}$, 5.20 $\times$ 10$^4$ M$^{-1}$ s$^{-1}$ and 6.70 $\times$ 10$^3$ M$^{-1}$ s$^{-1}$ in the gas phase, pentyl ethanoate, and DMSO, respectively), while it can exert good activity with $k_{overall} = 1.01 \times 10^9$ M$^{-1}$ s$^{-1}$ in water at physiological pH. The H-abstraction at the O5–H bond following the FHT pathway decides the HOO$^*$ radical trapping of SW in the lipid media, while SET dominates in polar environments, as expected for a weak acidic compound. Compared with Trolox, the rate constant of the HOO$^*$ + SW reaction in the lipid medium is slightly lower, whereas in an aqueous solution, it is about 78 times higher. The results of the calculations are in line with experimental results and suggest that SW is a promising natural free radical scavenger in an aqueous physiological environment.

4. EXPERIMENTAL AND COMPUTATIONAL METHODS

4.1. ABTS** Radical Scavenging Activity

The ability of compounds to scavenge the ABTS** radical is performed according to the method described previously.$^{23}$ The ABTS** radical cation is generated by mixing an aqueous solution of potassium persulfate (2.45 mM) and ABTS (7 mM) in the dark at room temperature for 12–16 h before use. The solutions of ABTS** were diluted in ethanol to give the working solution with an absorbance of 0.70 ± 0.02 at 734 nm. SW, which was isolated from R. harmandiana (Table S2, Supporting Information), was dissolved in DMSO 100% and diluted into concentrations from 0.006 to 1.0 mg/mL. Then, 190 µL of the working solution of ABTS** was mixed with 10 µL of samples at different concentrations, and the absorbance was measured at a wavelength of 734 nm. Trolox at 0.625, 1.25, 2.5, 5.0, and 10 µg/mL was used as a positive control. The percentage of radical inhibition was calculated using the following formula

\[
\% \text{ inhibition} = 100 - \frac{A_c}{A_n} \times 100\%
\]

where $A_c$ is the absorbance of the negative control (containing all reagents except the tested compound) and $A_n$ is the absorbance of the tested sample. The IC$^{50}$, which is the concentration of the sample at which the sample would inhibit the free radical by 50%, was calculated.

4.2. Computational Methods.

All density functional theory (DFT) calculations were carried out with the Gaussian 09 suite of programs.$^{31}$ The M06-2X functional$^{32}$ and the 6-311+G(d,p) basis set were used for all calculations. The M06-2X functional offers one of the most reliable methods to study thermodynamics and kinetics of radical reactions.$^{17,30,31,34,36,42,43}$ The kinetic calculations were performed following the QM-ORSA protocol.$^{49,50}$ Following the literature,$^{47,51,44-49}$ and are shown in Table S1, Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c04569.

Thermodynamic parameters, Cartesian coordinates, and frequency and energies of all of the transition states in the studied environments (PDF)

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Notes

The authors declare no competing financial interest.

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