



Theoretical and kinetic study of the singlet oxygen quenching reaction by hesperidin isolated from mandarin (*Citrus reticulata*) fruit peels

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Abstract

Antioxidants act as quenchers or scavengers of oxidative free radicals and singlet oxygen ($^1\text{O}_2$); these compounds are effective in the treatment of diseases associated with oxidative stress and food preservation. We studied the antioxidant activity of hesperidin which was isolated from mandarin (*Citrus reticulata*) fruit peels against singlet oxygen ($^1\text{O}_2$). High-performance liquid chromatography with diode array detection was used for chemical characterization. The total singlet oxygen quenching rate constants of the hesperidin was measured by using the Stern–Volmer model. Results showed an overall quenching rate constant with a value of $6.43 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for $^1\text{O}_2$, which for the best of our knowledge has not been reported before. Furthermore, quantum chemical calculations were performed to get insight into the molecular and electronic structure properties of this antioxidant, which confirms that the quenching mechanism through energy transfer is rarely probable and that $^1\text{O}_2$ could interact with the methoxy phenyl charge rich fragment of the molecule.

Keywords Singlet oxygen · Antioxidant · Hesperidin · Stern–Volmer model · Citrus reticulata

Introduction

The world population is growing every year at an exponential rate, likewise, the production of waste, especially from agricultural and urban activities (Marzo et al. 2019; Senthilkumar et al. 2020). In this sense, the recycle of agro-industrial waste represents an option to transform it into new raw materials that is emerging as an alternative to obtain compounds with beneficial properties for human health. The valorization of agro-industrial waste and the subsequent production of antioxidant substances is of great importance

due to the growing demand for natural antioxidant products, while at the same time, a sustainable and environmentally friendly alternative for waste treatment is being developed (Larios-Cruz et al. 2019). The chemical and biological characteristics of agro-industrial waste depend on the transformation process and the raw material used in the initial process. For fruits, as well as their residues, it is known as a rich composition in phenolic compounds and flavonoids (Mannino et al. 2020; Pereira et al. 2018).

In an oxidation reaction, a reactive oxygen species cause several chain reactions, which may disrupt biomolecules

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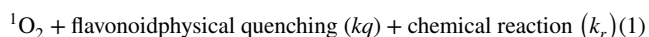
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(Bonnefont-Rousselot et al. 2011; Buonocore et al. 2010). An antioxidant is able to delay the oxidation of many compounds (e.g., carbohydrates, proteins and lipids) (Papas 1999; Neha et al. 2019; Sindhi et al. 2013). Natural antioxidants are used routinely in food to protect it against oxidation (Xu et al. 2017; Jayathilakan et al. 2007). The synthetic antioxidants (e.g., hydroxytoluene, butylated hydroxyanisole) act as quenchers of singlet oxygen ($^1\text{O}_2$) (Fatima et al. 2016; Bisby et al. 1999). However, synthetic antioxidants have health concerns due to their potential carcinogenic activity (Augustyniak et al. 2010). Currently, there is a substantial motivation to obtain and utilize antioxidants from natural sources because they are presumed to be safe from different points of view (Lourenço et al. 2019). $^1\text{O}_2$ can react with a large number and important biological molecules (e.g., proteins, DNA and lipids) (Miyamoto et al. 2014), thus, research on quenching singlet oxygen generation is a constant topic of interest. Different reports verified that flavonoids and their derivatives could effectively act as scavengers of $^1\text{O}_2$. The physical and chemical quenching are the two types of mechanisms for the $^1\text{O}_2$ quenching (Racine and Auffray 2005), each mechanism has a specific rate constant value (k_q =physical quenching, k_r =and chemical reaction). Conventional measurement of global quenching rates k_Q ($k_Q=k_q+k_r$) are reported in the literature (Diaz-Urbe et al. 2015a):



where the former (k_q) mechanism results in energy transfer but no chemical change in the energy acceptor. The (k_r) results in modification of the antioxidant. (Ray et al. 2013; Sjöberg et al. 2016; Davies 2003). The $^1\text{O}_2$ ($^1\Delta_g$) reactivity toward a certain biological objective will depend on the cell's ability to cope with oxidative damage and the concentration of antioxidants present. Only those electron-rich antioxidant substrates can compete with the solvent deactivation pathway since the $^1\text{O}_2$ ($^1\Delta_g$) lifetime within the cell is too small. This means that global values of quenching rates ($k_Q=k_r+k_q$) should be much higher than $10^6 \text{ M}^{-1} \text{ s}^{-1}$ value. Figure 1 compares the global rate constants (k_Q) of some synthetic and natural compounds that act as antioxidants.

Hesperidin is a flavanone glycoside, see Fig. 2 (Goliotmytis et al. 2014). It is an abundant and inexpensive natural product widely found in different citrus species (Devi et al. 2015).

Over time, hesperidin has become relevant because a large number of studies describe new pharmacological activities, with molecular objectives and mechanisms of action, it has anti-carcinogenic, anti-allergic and antioxidant properties. Matias et al. reported the effects of hesperidin as neuroprotective agent; this study confirmed its protective effects by normalizing oxidative stress and inflammation

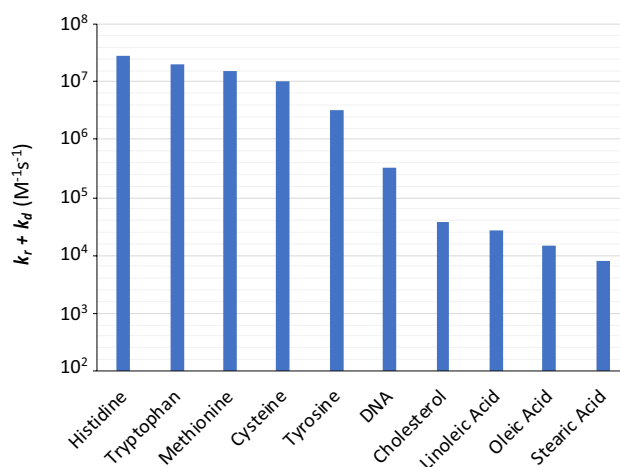


Fig. 1 Global quenching rate constants ($k_r + k_q$) of some relevant molecules against $^1\text{O}_2$ (Alarcón et al. 2010; Devasagayam et al. 1991; Nagai et al. 2005; Morales et al. 2012)

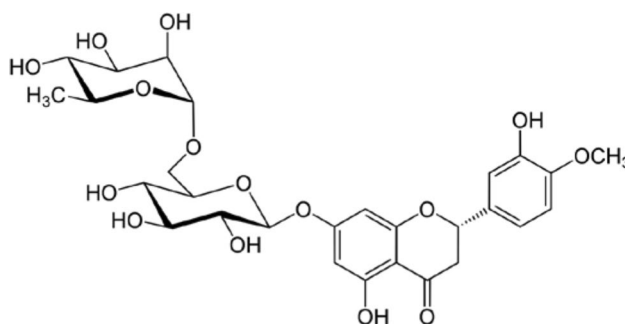


Fig. 2 Chemical structure of hesperidin

(Matias et al. 2017). The antioxidant activity and mechanisms of scavenging reactive oxygen species by hesperidin has been reported by different authors (Balakrishnan and Menon 2007; Bigoniya and Singh 2014; Pari et al. 2015). However, there is no information on the mechanisms of interaction of this molecule with singlet oxygen, as well as their kinetic parameters. In the present work, we studied the relative singlet oxygen quenching abilities of hesperidin isolated from *Citrus reticulata* peels and besides, the first singlet and triplet states (T_1) of hesperidin were determined using DFT and TD-DFT approaches.

Experimental

Reagents and standards

All reagents used in this work were commercially acquired, ACS grade, such as acetic acid glacial ($\geq 99.7\%$, Sigma-Aldrich), acetone ($\geq 99.5\%$, Sigma-Aldrich), methanol ($\geq 99.8\%$, Sigma-Aldrich), phosphoric acid ($\geq 85\%$,

Sigma-Aldrich), Rubrene (99.99%, Sigma-Aldrich), Sodium Molybdate dihydrate (99.9%, Sigma-Aldrich). Besides, certified standards were used: hesperidin (97%, Sigma-Aldrich). UV–Vis and FT-IR (KBr) spectra were obtained by Hewlett-Packard 8453 spectrophotometer, Bruker Tensor 27 spectrometers.

Isolation and characterization of hesperidin

The peels of the *C. reticulata* fruit previously washed and dehydrated (60 °C, 24 h) were cut into small pieces (ca. 4 mm²), which (50 g) were defatted with petroleum ether (peels:solvent ratio, 1:3) using the Soxhlet method (reflux, 18 h). Once defatted peels were dried, they were subjected to ultrasound-assisted extraction (three times) by means of ultrasonic bath (Ney 57H ULTRASONIK, 330 W 48 kHz) at 60 °C during 60 min (at 30 min intervals), with ethanol (1:3 ratio), to obtain a flavonoid-rich fraction (Bousbia et al. 2009; Ghafoor 2009). This fraction was dried in vacuum to dryness. From the flavonoid-rich fraction, hesperidin was isolated using a modified method based on the procedures described by Dickson, and Nipornram et al. (Nipornram et al. 2018; Singanusong et al. 2015). In short, 1 g of ethanol extract was mixed/completely dissolved in 10% acetic acid by sonication at 50 °C (10 min). After that, hesperidin precipitated as a pale yellowish powder, which was centrifuged to separate it, and then the powder was washed with hot acetone and recovered as a white solid, which was structurally characterized (m.p., UV, IR). Subsequently, the purity of the isolated hesperidin was determined by means of liquid chromatography and by comparison with the certified standard of hesperidin. The chemical analysis was carried out in a RP-HPLC–DAD (UHPLC Ultimate 3000, Dionex—Thermo Fisher Scientific, Inc.; DAD, UV/Vis) equipped with a Capcell-Pak[®] C₁₈ UG120 S-5 column (C₁₈-bonded silica gel, 120 Å, 5 µm, 250 mm × 4.6 mm I.D, Shiseido Co, Tokyo); for the elution, a mobile phase (flow: 1 mL/min) constituted by methanol (solvent A—20–95%) and 0.25% phosphoric acid (solvent B—80–5%) programmed as a linear gradient, was used. The selected wavelengths (λ_{max}) for detection were 250 nm, 285 nm, 320 nm, and 355 nm. Data acquisition and processing were supported with the Chromeleon[®] 7 Chromatography Data System software (Version 7.2.1.5833, Thermo Fisher Scientific, Inc.).

Singlet oxygen generation and kinetic study

Singlet oxygen was generated by using methodology proposed by Aubry and Bouttemy (Nardello et al. 1999). In short, the overall rate constant $k_Q = (k_q + k_r)$ for the reaction of ¹O₂ with hesperidin was determined in ethanol solution at 25 °C through competition reaction method using Rubrene as standard compound and analyzing the first-order rate constant (S) of

the decay curve of Rubrene. ¹O₂ was induced from dark chemical reaction of Sodium Molybdate and hydroxide peroxide. The overall rate constant was determined using a Stern–Volmer plot derived from steady state kinetics. The reciprocal life times were represented as a function of the hesperidin concentration and the bimolecular rate constants were determined from the slope of the linear plots. Rubrene oxidation with a chemical source of singlet oxygen in microemulsion was performed to check singlet oxygen quenching activity (Lee and Jung 2010). The microemulsions were prepared at temperature (298 K) by adding an aqueous solution of 0.2 M Na₂MoO₄·2H₂O (290.4 mg in 6 mL of water) dropwise to a magnetically stirred slurry solution of SDS (4.7 g), 1-Butanol (9.4 g), and methylene chloride (60 mL). After a few minutes, the turbid suspension was converted into a mobile and transparent liquid. Then, 2.0×10^{-4} mol of rubrene was introduced into a small Erlenmeyer flask plus 15 mL of microemulsion. The medium was magnetically stirred for 10 min and stored in darkness to prevent the autosenitized photo oxidation of Rubrene. After that, 50 mmol of H₂O₂ were added to the red solution and the reaction medium was stirred with a microscale magnetic bar at room temperature. The samples solutions also contained PAPs (as quenchers, $0\text{--}3.0 \times 10^{-3}$ M). The oxidation of Rubrene was monitored using visible spectroscopy at 522 nm (Diaz-Urbe et al. 2015a).

Quantum chemical calculations

Geometry optimization of the electronic ground states of hesperidin was performed using the B3LYP functional (Becke 1998, 1993; Lee 1988) and the 6–31 + g(d,p) basis set as implemented in the Gaussian 09 package (Frisch et al. 2009). The minima of the first singlet and triplet states (T_1) of hesperidin were determined using the time-dependent DFT (TD-DFT) approaches. Corrections to the dispersion energy were taken into account in all geometry optimizations using the Grimme approaches (DFT-D3) (Grimme and Waletzke 1999). Harmonic vibrational frequencies were computed numerically to establish the structures as minima points in the potential energy surface. The adiabatic excitation energy of the first T_1 state of hesperidin was obtained from geometry optimization computation. The vertical excitation energies were computed in the framework of TD-DFT method. Implicit solvation effects were incorporated using the polarized continuum model (PCM, $\epsilon = 24.5$) for ethanol (Schäfer et al. 2000; Klamt and Schüürmann 1993; Reichardt and Welton 2010). The nature of the electronic transitions has been elucidated in terms of the electron density difference maps (EDDMs), which were computed and drawn with GaussSum (v. 2.2.6) (O’Boyle et al. 2008).

Results and discussion

Characterization of isolated hesperidin

Once the ethanol extract and hesperidin was obtained from the tangerine peels by sonication, the yield and/or content (flavonoid) was calculated. As a result, the flavonoid-rich extract presented a yield of $7.4 \pm 0.4\%$ (on a dry basis), and the content of isolated hesperidin (mg) per gram of dry extract was 98 ± 0.4 mg/g. The qualitative chemical analysis by HPLC–DAD (λ : 285 nm) of the isolated hesperidin (> 99%) is shown in Fig. 3, where the chromatogram spectrum of the ethanolic extract (Fig. 3a) and the chromatogram and UV absorption spectrum of hesperidin (Fig. 3b) isolated from mandarin fruit peels are compared. The retention times obtained for (R_t : 16.55 min) and UV absorption spectra (main λ_{\max} : 230 nm, 284 nm, 328 nm) of both samples match with the reported for the commercial standard. Likewise, the IR spectra for the two samples were corresponding to each other; i.e., the characteristic absorption bands [ν : $3420\text{--}3381$ cm^{-1} and 1356 cm^{-1} (–OH); $2938\text{--}2916$ cm^{-1} (–CH_{alip}) and $1605\text{--}1516$ cm^{-1} (–C=C–CH–); 1645 cm^{-1} (–C=O); $1277\text{--}1242$ cm^{-1} (–C_{Ar}–O–); $1130\text{--}1094$ cm^{-1} (–C_{alip}–O–); $1065\text{--}1049$ cm^{-1} (–OCH₃)] were similar.

In addition, the melting points measured for the two samples was $248\text{--}250$ °C (isolated hesperidin) and $250\text{--}252$ °C (certified standard of hesperidin), respectively; these values are included in the range ($250\text{--}262$ °C)

reported in the consulted literature for other reports (Book and Hesperidin 2019; Hassan et al. 2018).

k_Q value for the quenching of $^1\text{O}_2$ by Hesperidin

Figure 4a shows the kinetics results for the chemical trapping of rubrene with singlet oxygen in the presence and absence of hesperidin. In all cases, the reactions were fitted to the pseudo-first-order kinetics. Results show direct proportionality between hesperidin concentration and its antioxidant capacity to act as a singlet oxygen quencher.

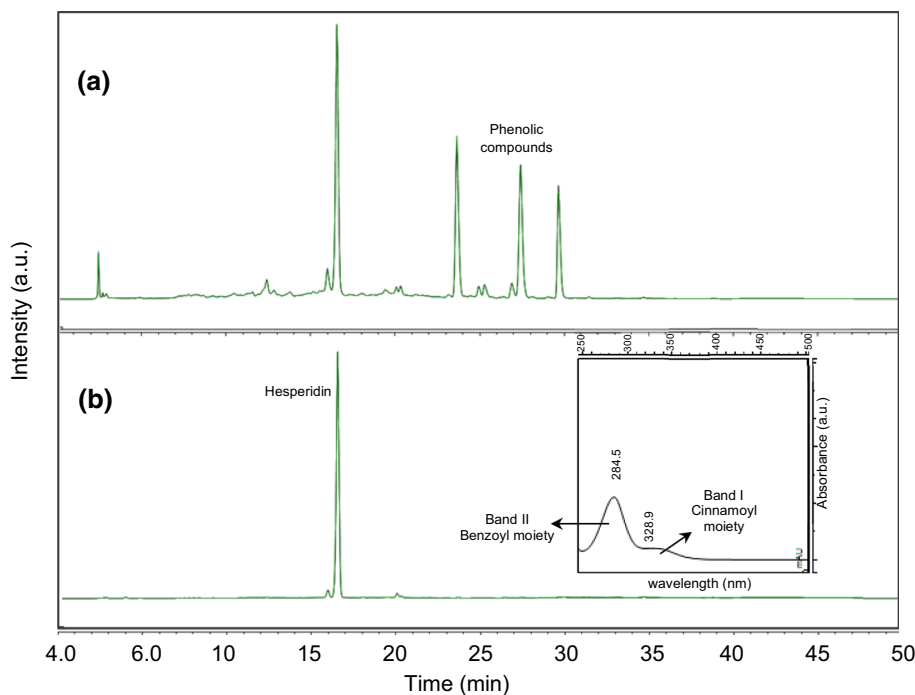
The k_Q value for the reaction of singlet oxygen with hesperidin in ethanol were determined according to (1) (Hocman 1988):

$$\frac{S_o}{S_s} = 1 + \left[\frac{k_q + k_r}{k_d} \right] [\text{Hesperidin}] \quad (1)$$

S_0 and S_S correspond to the slope of the disappearance of singlet oxygen (acceptor) first-order plots, in the absence and presence of hesperidin, see Fig. 4a. The rate of deactivation of singlet oxygen (k_d) in ethanol has a value of 8.3×10^4 s^{-1} (Merkel and Kearns 1972). Figure 4b shows the plot of S_0/S_S vs concentration of hesperidin. Applying this methodology, the k_Q value obtained for hesperidin was 6.43×10^7 $\text{M}^{-1} \text{s}^{-1}$, furthermore Table 1 lists the k_Q values for previously reported antioxidants.

The herein obtained results indicate that hesperidin rate constants (k_Q) is similar to the values reported for flavonoids in ethanol like chrysin (2.01×10^7 $\text{M}^{-1} \text{s}^{-1}$), apigenin

Fig. 3 Chromatographic profile by HPLC–DAD of the: **a** the ethanolic extract and **b** hesperidin isolated from mandarin fruit peels, (inside; UV–Vis absorption spectrum of the hesperidin obtained from mandarin fruit peels)



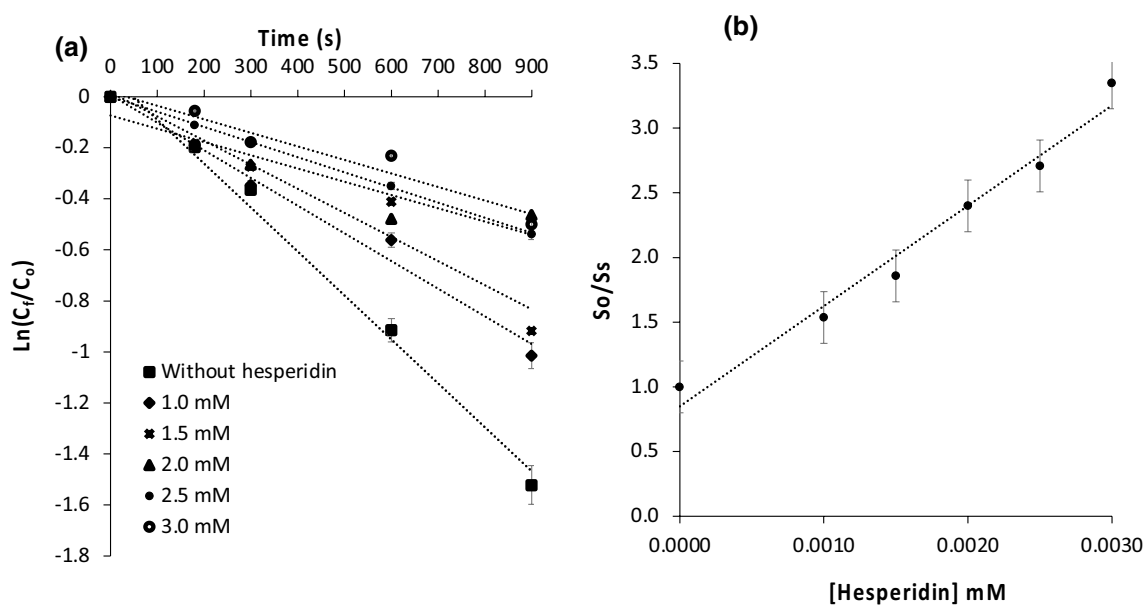


Fig. 4 **a** Plot of $\ln(C_t/C_0)$ versus Time as a function of hesperidin Concentration (mM). **b** Plot of S_0/S_s vs concentrations (mM) of hesperidin

Table 1 Global kinetic rate values (k_Q) reported in the literature for typical antioxidants

Antioxidant	$k_Q \times 10^7$ ($M^{-1} s^{-1}$)	Reference
Chrysin	2.01	Sjöberg et al. (2016)
Apigenin	2.84	Nagai et al. (2005)
Catechins	10.9–14.7	Ouchi et al. (2010)
<i>tert</i> -butyl-hydroxy-anisol	3.37	Miyamoto et al. (2014)
<i>tert</i> -di-Butyl-hydroxy-toluene	0.43	
Naringenin	0.37	Diaz-Urbe et al. (2016)
Naringin	2.1	

($2.84 \times 10^7 M^{-1} s^{-1}$), catechins ($1.09 \times 10^7 - 1.47 \times 10^8 M^{-1} s^{-1}$). Hesperidin has similar singlet oxygen quenching activity as previously reported synthetic antioxidants like *tert*-butyl-hydroxyanisole ($3.37 \times 10^7 M^{-1} s^{-1}$) and *tert*-di-Butyl-hydroxytoluene ($4.26 \times 10^6 M^{-1} s^{-1}$). Reports of k_Q for similar antioxidants such as naringenin (where the glycoside rings are replaced by Hydroxyl groups) show smaller k_Q values, as the ones reported in this work (see Table 1). The herein obtained result indicate that the quenching rate increases with increasing number of $-OH$ substituents (over the glycoside rings), that is, the electron-donating capacity of these flavonoids (Diaz-Urbe et al. 2016). Other similar structure to hesperidin is naringin, differentiating between them due to the presence of a methoxy group and the location of the hydroxyl group in the B-ring into the hesperidin structure, a value of $2.1 \times 10^7 M^{-1} s^{-1}$ was previously reported for the k_Q for naringin. Thus, the overall rate

constants k_Q for hesperidin is three times larger than the k_Q value reported for naringin. These results suggest that besides of the substituents into the flavone skeleton, the substituents in the B-ring directly affects the quenching activity of the hesperidin, thus the existence of methoxy group in the B-ring increased the antioxidant activity. Currently, research has been focused on the analysis of the antioxidant capacity of extracts from agro-industrial wastes due to their content of secondary metabolites (e.g., phenols, flavonoids, anthocyanins, and carotenes).

The exponential growth of the world population implies continuous increasing in the production agro-industrial wastes, especially from agricultural and urban activities. This situation presents an important opportunity for natural products (such as the residues of the mandarin peel) as a secondary source of compounds with high added-value (Lemes et al. 2016; Fierascu et al. 2019; Sath et al. 2018). The agro-industrial waste represents an option to transform it into new raw materials that are emerging as an alternative to obtain compounds with beneficial properties for human health. The valorization of agro-industrial waste for the production of antioxidant substances is of utmost importance due to the growing demand for natural antioxidant products, while providing a sustainable and environmentally friendly alternative for waste treatment (Castro-Vargas et al. 2019; Toop et al. 2017).

Computational study

The optimized ground S_0 and T_1 state minima of hesperidin at the B3LYP-D3/6–31 + G(d,p) level are presented in

Fig. 5. Both geometries, S_0 and T_1 show the sugar group and substituted phenyl group out of the plane of the fused rings fragment. As can be observed in Fig. 5, the dihedral angles indicated by yellow and green circles show differences of around 10 and 5 degrees, respectively. The computations results provide adiabatic energy value of the T_1 state of 2.91 eV, which is a value above of the reported energy for singlet oxygen of 0.98 eV (Diaz-Urbe et al. 2015b).

This energy difference represents a pronounced endergonic process which indicates that energy transfer is not able to occur due to the very high barrier. Therefore, it is expected that the mechanism of quenching of the reactive oxygen species generation be through a chemical reaction process. On the other hand, the chemical reactivity indexes were calculated in the framework of Koopmans theory. The estimated chemical potential (μ) is -4.02

which represents the infinitesimal change of energy, when electronic charge is added to a molecular system at a constant external potential of the nuclei ($v(r)$), fact closely related with its electronegativity (χ). Chemical hardness (η), and electrophilicity (ν) observed values are 2.32 and 3.48, respectively. The HOMO and LUMO energies for this compound are -6.33 and -1.70 eV. These magnitudes show the same tendency than others efficient quenchers reported by our group (Diaz-Urbe et al. 2015b), which have shown similar antioxidant properties as flavonoids acting as source of electrons which enhance their antioxidant activity. To go further in the electronic structure description of hesperidin, we also analyzed the condensed Fukui functions. Figure 6 shows the wave functions for nucleophilic (f^+) and electrophilic (f^-) attacks. Considering the information provided by the Fukui functions, the

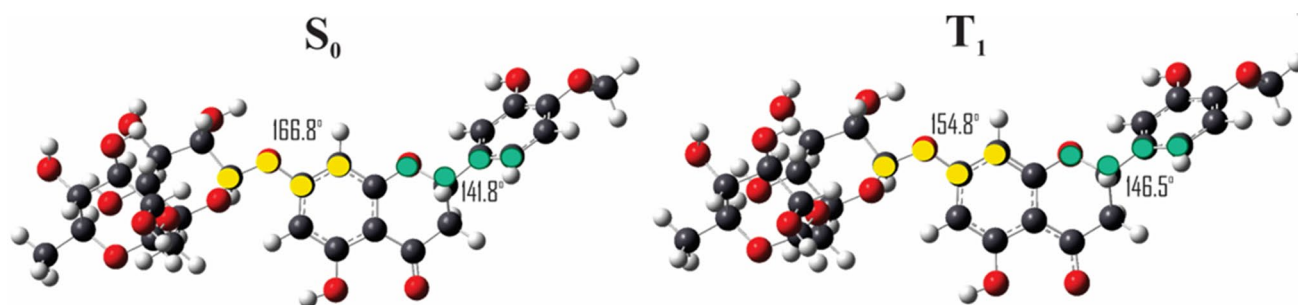


Fig. 5 Molecular structure of the ground state (S_0) and the first triplet (T_1) state of hesperidin

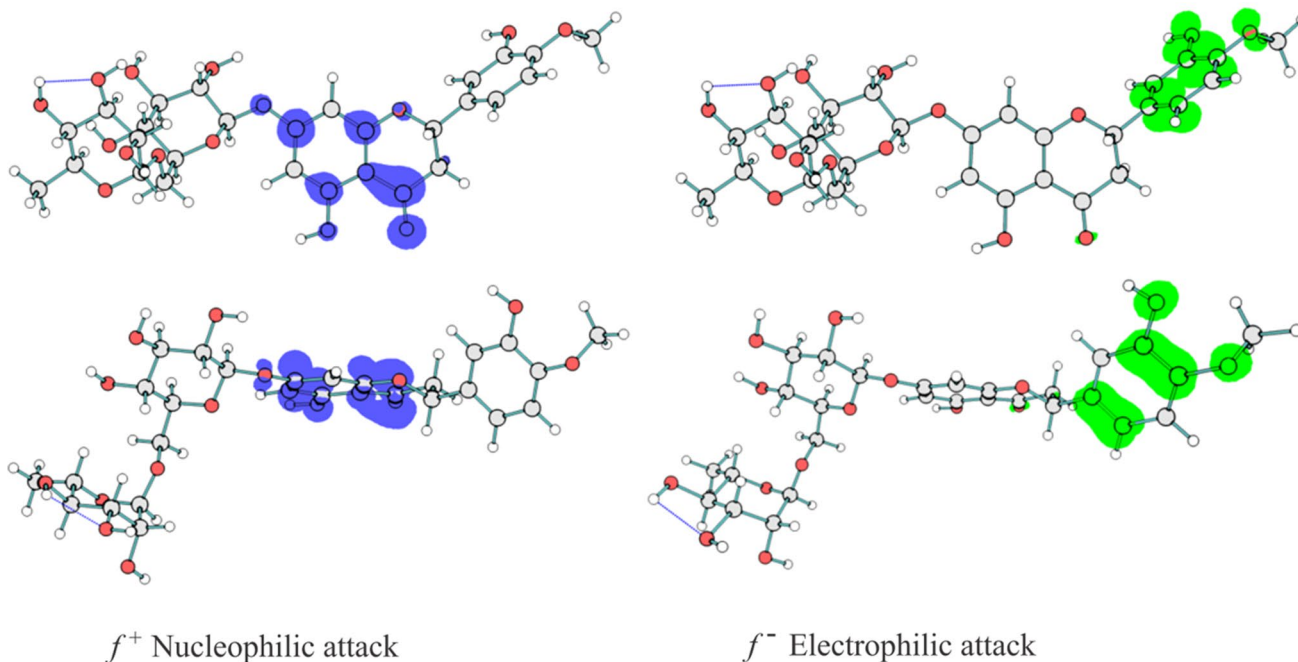


Fig. 6 Condensed Fukui functions for nucleophilic (f^+) and electrophilic (f^-) attacks for compounds

singlet oxygen which preferable attacks high electron density sites, could interact with the ring holding the methoxy group which is the fragment for electrophilic attack, being thus a feasible pathway for chemical quenching process.

On the other hand, the theoretical characterization of the corresponding excited states involved in the absorption bands of the UV–Vis spectrum was carried out. The results provided by the simulations are in great agreement with the experimental reported data, as the wavelengths show slight shifts as can be found in Table 2. Another worthy fact to mention is that the oscillator strengths (f), which is related to the probability of this transition to occur, which exhibit the same tendency as the intensities of the bands in the spectrum profile.

The molecular orbitals (MOs) that form the configurations for these transitions are mainly HOMO, HOMO-1, HOMO-2, LUMO, among others. In this sense, to show the changes in the electron density localization involved in the excitations, the electron density difference maps (EDDMs) were plotted (Fig. 7). From these maps it is possible to

observe more charge migration upon photo absorption in the electron excitation of band 3 followed by band 1.

Conclusions

The antioxidant activity of hesperidin isolated from mandarin (*Citrus reticulata*) fruit peels as a source of natural antioxidant against singlet oxygen ($^1\text{O}_2$) was studied. The k_Q value for $^1\text{O}_2$ quenching reported for hesperidin was $6.43 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, this value is suitable compared to develop practical applications to both synthetic and natural antioxidants. The DFT simulations *i.e.*, the electronic ground and excited states calculations of hesperidin, suggested that there is a high energetic barrier to lead a physical quenching of $^1\text{O}_2$ so, the mechanism could mostly follow the chemical quenching pathway. In this regard, it was found that the $^1\text{O}_2$ could be able of attacking the ring holding the methoxy group of the hesperidin compound.

These results may contribute to the development of natural products (including food waste and residues) with

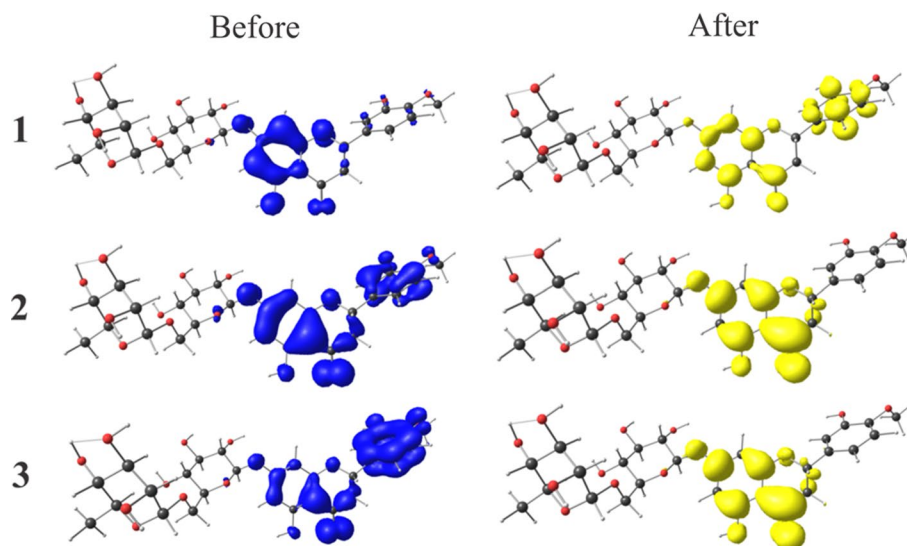
Table 2 TD-DFT vertical excitation energies (in nm) of hesperidin in ethanol solution employing PCM solvation model

	$\lambda_{\text{abs}}^{(a)}$ nm(eV)	$\lambda_{\text{abs}}^{(b)}$ nm(eV)	F	Active MO	Contr. %
1	200	203	0.720	HOMO-1 \rightarrow LUMO+2	22.5
				HOMO-1 \rightarrow LUMO+3	21.2
				HOMO-8 \rightarrow LUMO	24.6
2	285	261	0.377	HOMO-2 \rightarrow LUMO	10.9
				HOMO-1 \rightarrow LUMO	76.1
3	329	330	0.002	HOMO-2 \rightarrow LUMO	25.7
				HOMO-1 \rightarrow LUMO	28.6
				HOMO \rightarrow LUMO	24.6

Oscillator strengths f and the active molecular orbitals involved in the transitions are also reported

(a) Experimental. (b) Theoretical

Fig. 7 EDDMs for hesperidin upon photoexcitation to the first singlet excited state calculated using the B3LYP+D3/6-31+g(d,p) wave functions. The blue densities represent the charge concentration, and the yellow densities represent the target location after electron transfer



potential applications in reducing oxidative damage involving reactive oxygen species in living organisms and in food preservation.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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