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Original article

A theoretical antioxidant pharmacophore for resveratrol

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ABSTRACT

The structure–activity relationship has been used to study the determination of antioxidant pharmacophore for resveratrol using quantum chemistry calculations by the Functional of Density Theory method. According to the geometry obtained by using a B3LYP/6-31G*, the HOMO, ionization potential, bond dissociation energies, stabilization energies, and spin density distribution, the electron or hydrogen abstraction in *para* position is more favored than in *meta* positions for resveratrol and related derivatives because of the resonance effects. Comparison with structurally related compounds revealed that the antioxidant pharmacophore of resveratrol is 4-hydroxystilbene. Spin distribution showed that the π-type electron system determines the stability of radicals and the unpaired electrons are mainly distributed to the O-atom in *para* position, double bond, and B-benzene ring. The antioxidant activity of resveratrol is related to the stabilization energy of 4-hydroxystilbene in resveratrol hydroxylated derivatives. Furthermore, the results explain the activity difference between resveratrol and its hydroxylated derivatives.

1. Introduction

Resveratrol or 3,5,4′-trihydroxy-*trans*-stilbene (Fig. 1) is a natural phytoalexin that is present in grapes and many other plants. It was found recently that this compound possesses a variety of biological activities [1–11]. Resveratrol has shown to posses cancer chemo-preventive activity [3,4]. Therefore, the past several years have witnessed intense research devoted to the biological activity, especially the antioxidant activity, of this compound [4–11], since free radical-induced peroxidation of membrane lipids and oxidative damage of DNA have been considered to be associated with a wide variety of chronic health problems, such as cancer, atherosclerosis and aging [12,13], and gene transcription can be regulated by oxidants, antioxidants and other determinants of the intracellular redox state. Resveratrol has been reported to be a good antioxidant against the peroxidation of low-density lipoprotein (LDL) [8] and liposomes [9], a potent inhibitor of lipoxygenase [10], and is able to protect rat heart from ischaemia reperfusion injury [11].

The antioxidant activity of resveratrol is related to its hydroxyl (OH) groups which can scavenge free radicals produced in vivo [14]. The experimental data demonstrate that the molecules which H-atoms of three OH groups are all replaced by CH_3 group or without the three OH groups lose their antioxidant activity. Stivala used the thermodynamic parameters, the formation enthalpies (ΔH_f) calculated by semiempirical method PM3, to discuss the antioxidant activity of *cis*-resveratrol and *trans*-resveratrol [4]. However, in general, the PM3 method cannot give the fine geometry and unpaired electron distribution of a molecule. In contrast, DFT has proved to be reliable in the study of energetic and geometrical properties of proton transfer and other ion–molecule reactions [15–18].

In a previous work, Cao and co-workers have investigated the antioxidant activity of resveratrol by comparing the bond dissociation energies (BDE). The results showed that a hydrogen abstraction in the *para* position is more favored than in *meta* positions, showing that resveratrol is a potent antioxidant because its radicals have semiquinone structure in which the unpaired electrons are mainly distributed on the *para* position of the O-atom, the hydroxyl groups and the double bond contribute to the resveratrol oxidation [19].

Nevertheless, in general BDE studies determine global influence in molecular structure for a hydroxyl moiety, cannot give pharmacophoric group. Therefore, in this paper a systematic simplification of the molecular structure of resveratrol is used to determine the minimum structural characteristics necessary for antioxidant activity. The molecular simplification used on the antioxidant activity of resveratrol is investigated by the DFT method using the ionization potential (IP), highest occupied molecular orbital (HOMO), bond dissociation energies of hydroxyl group (BDE_{OH}), stabilization energies (ΔE_{iso}), and spin density distribution. The goal of the present study is to determine the pharmacophore responsible for antioxidant activity of resveratrol to be a useful and economical method to investigate antioxidant mechanism of molecules.

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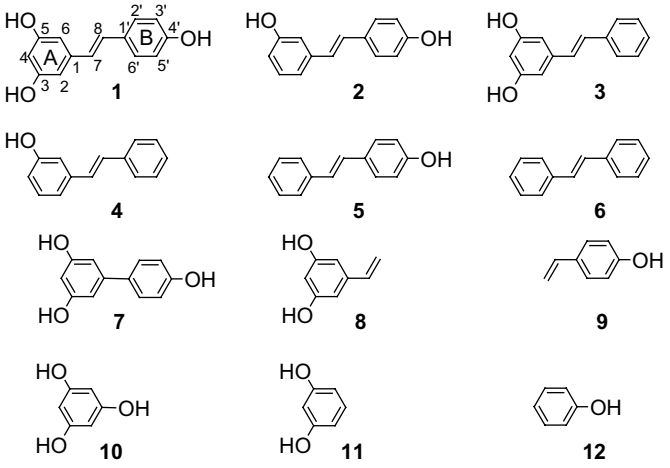

Fig. 1. Structure and numeration of resveratrol and related derivatives.

2. Methods

All the calculations were performed with the Gaussian 03 molecular package [20]. Prior to any DFT [21] calculations all structures were submitted to PM3 [22] geometry conformational search. All PM3 geometries were fully optimized at B3LYP hybrid density functional theory [23,24] by using a 6-31G* basis [25]. Only the conformation most stable for a given compound has been used. The IP was calculated as the energy differences between a neutral molecule and the respective cation free radical (Eq. (1)). The bond dissociation energies were calculated as the energy differences between a neutral molecule and the respective semiquinone plus hydrogen radical (Eq. (2)). Radical stability is usually been calculated by bond dissociation energies. In this case, the radical stability is determined by the stabilization energies' calculation, as showed in Eq. (3) for the hydrogen transfer (ΔE_{iso}), where resveratrol derivative is ArOH and phenol is PhOH.

$$IP = EArOH^{\bullet+} - EArOH \quad (1)$$

$$BDE = (EArO^{\bullet} + EH^{\bullet}) - EArOH \quad (2)$$

$$\Delta E_{iso} = (ArO^{\bullet} + PhOH) - (ArOH + PhO^{\bullet}) \quad (3)$$

In the present article we aim to explore the resveratrol structure and its hydroxylated derivatives for the pharmacophore antioxidant identification. In Figs. 1 and 2, the new compounds included resveratrol derivatives constructed by molecular simplification (**2**–**12**) and by hydroxyl addition on one stilbene structure (**13**–**17**), respectively.

We are interested in understanding the role played by the different structural features of this molecule and in obtaining new compounds endowed with better antioxidant properties.

We have therefore undertaken a systematic study of the influence of the hydroxyl group, alkene group, and/or aromatic ring on the antioxidant properties of resveratrol derivatives. To this aim, we have calculated: (i) highest occupied molecular orbital (HOMO); (ii) ionization potential (IP); (iii) bond dissociation energies (BDE); (iv) stabilization energies (ΔE_{iso}); (v) spin density.

3. Results and discussion

3.1. HOMO

The antioxidant activity of 17 different resveratrol derivatives and related compounds was theoretically measured. The selection of these compounds was based on their chemical structure characteristics. Some compounds were naturally occurring stilbene.

The frontier orbital energy, ε_{HOMO}, is an important parameter of molecular electron structure. The molecule which has the lower ε_{HOMO} has weak electron donating ability. On the contrary, the higher ε_{HOMO} implies that the molecule is a good electron donor [26]. The HOMO disposition of a phenolic compound can indicate its active site of scavenging free radicals qualitatively because of the H-abstraction reactions after electron transfer. The HOMO values are shown in Table 1.

The molecules with OH in *para* position showed HOMO values of −5.21 eV for resveratrol (**1**) and −5.22 eV for compound **2**. Similar result is expected for 4-hydroxystilbene (**5**), because of two hydroxyl substitutions. In fact, the HOMO value is −5.23 eV. Therefore, the result indicates that the hydroxyl change for hydrogen decreased HOMO values.

In contrast, the additional hydroxylation of resveratrolat positions 3′, 4′ and 5′ (compounds **13**, **15**–**17**) decreased HOMO values. Consequently, these compounds have more electron donating ability than resveratrol. Calculating HOMO values, the differences between analogues without catechol or pyrogallol groups and compounds with only one resorcinol group (compounds **15**–**16**) were found to be even less pronounced. The most nucleophilic compound in this theoretical was analogue **17** (HOMO value: −4.92 eV) followed by analogues **13**, **16** and **15** (HOMO value: −4.97 eV, −5.16 eV, and −5.19 eV, respectively). The results obtained in the present work indicate that the existence of a catechol or pyrogallol structure in the B-ring is essential for the increased HOMO values. The contribution from resorcinol in the A-ring also cannot be neglected. Further, in compounds **13** and **17**, the gallate ring also contributes remarkably to the increase in HOMO values. These results are in accordance with the experimental data of Murias and co-workers [28] for the relationships between cytotoxicity and antioxidant methods.

Nevertheless, the molecules with OH only in *meta* position showed HOMO values of −5.48 eV (**3**). This result is similar for compound **14** (−5.49 eV), with two resorcinol groups in A- and B-rings. The substitution of all hydroxyl gave stilbene (**6**) with HOMO value of −5.52 eV. This result is equal to compounds with the absence of alkene moiety (**7**). The phenol relevance can be demonstrated by removing A- or B-rings with HOMO values being

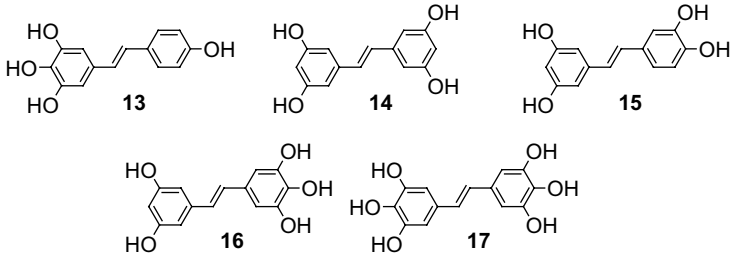

Fig. 2. Structure of hydroxylated resveratrol derivatives.

Table 1
Theoretical properties of resveratrol and related derivatives

Derivatives	HOMO (eV)	LUMO (eV)	IP (kcal mol^{-1})	BDE_{OH} (kcal mol^{-1})	ΔE_{iso} (kcal mol^{-1})
1	−5.21	−1.15	155.68	80.09	−5.84
2	−5.22	−1.18	156.02	80.69	−5.24
3	−5.51	−1.37	163.01	87.29	1.35
4	−5.48	−1.33	162.49	86.03	0.09
5	−5.23	−1.20	156.78	80.59	−5.34
6	−5.52	−1.37	164.05	–	–
7	−5.52	−0.69	165.62	83.35	−2.58
8	−5.81	−0.81	179.29	85.79	−0.15
9	−5.57	−0.58	173.36	82.55	−3.38
10	−5.84	0.59	183.98	87.22	1.28
11	−5.78	0.19	183.11	87.15	1.21
12	−5.96	0.03	189.17	85.15	0
13	−4.97	−1.06	149.37	79.83	−6.10
14	−5.49	−1.36	161.50	85.98	0.04
15	−5.19	−1.19	154.88	71.08	−14.85
16	−5.16	−1.21	153.94	65.73	−20.95
17	−4.92	−1.06	147.55	64.99	−21.18

−5.81 eV (**8**) and −5.57 eV (**9**), respectively. Furthermore, the styrene importance can be observed by removing A- or B-styrene groups. Its HOMO values are −5.84 eV for phloroglucinol (**10**), −5.78 eV for resorcinol (**11**), and −5.96 eV for phenol (**12**).

In the present work, the HOMO values for resveratrol derivatives have been studied. The increased HOMO values in order by withdrawal of HO in *meta* position < HO in *para* position < A-phenol ring < B-phenol ring < A-styrene group < B-styrene group < 4-hydroxystilbene. Nevertheless, additional HO in 3′ and 5′ positions of stilbene increased HOMO value. Therefore, considering the disposition of HOMO value, the additional HO group in *para* position of stilbene is easily attacked by the electrophilic agents, such as radicals or metal ions. In contrast, the additional HO group in *meta* positions of stilbene has little chance to react with agents.

3.2. Ionization potential (IP)

The ionization potential (IP) represents the ease of electron donation of resveratrol and related derivatives. The electron abstraction is the first antioxidant mechanism. Therefore, molecules with a lowest IP are more active. The IP values are shown in Table 1.

Our results showed the IP value for resveratrol (**1**) to be 155.68 kcal mol^{-1} and molecules with hydroxyl group in *para* position to have increased IP values, such as **2** (156.02 kcal mol^{-1}) and **5** (156.78 kcal mol^{-1}). Moreover, in molecules with hydroxyl group in *meta* position, such as **3** (163.01 kcal mol^{-1}) and **4** (162.49 kcal mol^{-1}), we have shown the highest IP values. However, the hydroxyl group is important for the electron-donating capacity. In fact, the hydroxyl change for hydrogen in all positions increased IP values for **6** (164.05 kcal mol^{-1}). Therefore, the hydroxyl absence showed increased IP values and decreased electron-donating capacity.

On the other hand, the IP values decreased in molecules with additional hydroxyl in *ortho* position to form catechol or pyrogallol groups, such as **13** (149.37 kcal mol^{-1}), **15** (154.88 kcal mol^{-1}), **16** (153.94 kcal mol^{-1}), and **17** (147.55 kcal mol^{-1}). Nevertheless, an additional hydroxylation in *meta* position increased the IP values, such as **14** (161.50 kcal mol^{-1}). Therefore, the additional hydroxyl in *ortho* position decreased IP values and increased the electron-donating capacity, but the additional hydroxyl in *meta* position increased IP values and decreased the electron-donating capacity. In these compounds, the antioxidant activity can be determined mainly by the stability of the cation free radical and these species are generated after electron abstraction. The electronic effect, such as inductive and/or resonance effects, is mainly responsible for the cation free radical stabilization. Therefore, the hydroxyl moiety in *para* position of stilbene is more reactive than *meta* position because of the resonance effect and its cation free radicals are formed with minor energy. The compounds with more resonance structure are more stable and showed the lowest IP values.

In fact, the alkene substitution showed value of 165.65 kcal mol^{-1} for the biphenyl compound (**7**). The phenol importance can be confirmed by removing A- or B-rings with IP values of 173.36 (**9**) and 179.30 kcal mol^{-1} (**8**), respectively. Therefore, the styrene importance can be confirmed by removing styrene group, with IP values of 183.98 (**10**), 183.11 (**11**), and 189.17 kcal mol^{-1} (**12**).

3.3. Bond dissociation energy (BDE)

The bond dissociation energies (BDE_{OH}) for resveratrol derivatives with different OH substitutions were calculated. This value represents the ease of hydrogen donation of resveratrol and related derivatives to give semiquinone derivatives. The hydrogen abstraction is the main antioxidant mechanism studied [16–19]. Therefore, molecules with a lowest BDE_{OH} are more active. The BDE_{OH} values are shown in Table 1.

As can be seen from Table 1, BDE_{OH} value for resveratrol (**1**) is 80.09 kcal mol^{-1}. Molecules with OH in *para* position had increased BDE_{OH} values, such as **2** (80.69 kcal mol^{-1}) and **5** (80.59 kcal mol^{-1}). Moreover, molecules with OH in *meta* position had increased BDE_{OH} values, such as **3** (87.29 kcal mol^{-1}) and **4** (86.03 kcal mol^{-1}). Nevertheless, an additional OH in *para* position decreased BDE_{OH} values, such as **13** (79.83 kcal mol^{-1}), **15** (71.08 kcal mol^{-1}), **16** (65.73 kcal mol^{-1}), and **17** (64.99 kcal mol^{-1}). Moreover, the BDE_{OH} values increased in molecules with additional OH in *meta* position, such as **14** (85.98 kcal mol^{-1}). These results show good tendency with HOMO and IP values.

These results showed that antioxidant activity can be determined mainly by the stability of the semiquinone radical, generated after hydrogen abstraction. The bond dissociation energies in molecules with HO group in *para* position of stilbene are formed with minor energy than in *meta* position. The high electron transfer found for hydrogen abstraction in *para* position is facilitated by the existence of the π-delocalized system between B- and A-rings (see Fig. 3). Hydrogen abstraction in the *meta* position is complicated by the inexistence of the π-delocalized system between B- and A-rings (see Fig. 4). The hydrogen abstraction in *para* position gave compounds with more resonance structure. In opposition, the hydrogen abstraction in *meta* position gave compounds with less resonance structure.

In accordance with ionization potential is expected a reduction of BDE_{OH} value for the alkene substitution. In fact, the value is 83.35 kcal mol^{-1} for the biphenyl compound (**7**). The phenol importance was also confirmed by removing A- or B- rings with BDE_{OH} values of 82.55 (**9**) and 85.79 kcal mol^{-1} (**8**), respectively. Similar result that is expected for the styrene importance was also confirmed by removing styrene group, with BDE_{OH} values of 87.22 (**10**), 87.15 (**11**), and 85.15 kcal mol^{-1} (**12**). Therefore, the absence of alkene moiety decreased the number of resonance structures for the semiquinone radical and antioxidant activity.

These results have importance because lipid peroxidation can be inhibited in the presence of various antioxidants which can act at different processes [27]. The chain-breaking antioxidants are one of the antioxidant types which inhibit the process of lipid peroxidation by scavenging the free radicals such as lipid peroxyl radicals, LOO$^{\bullet}$, converting them into long-lived and less reactive radicals mainly in propagation and termination steps. This is shown in Eq. (4).

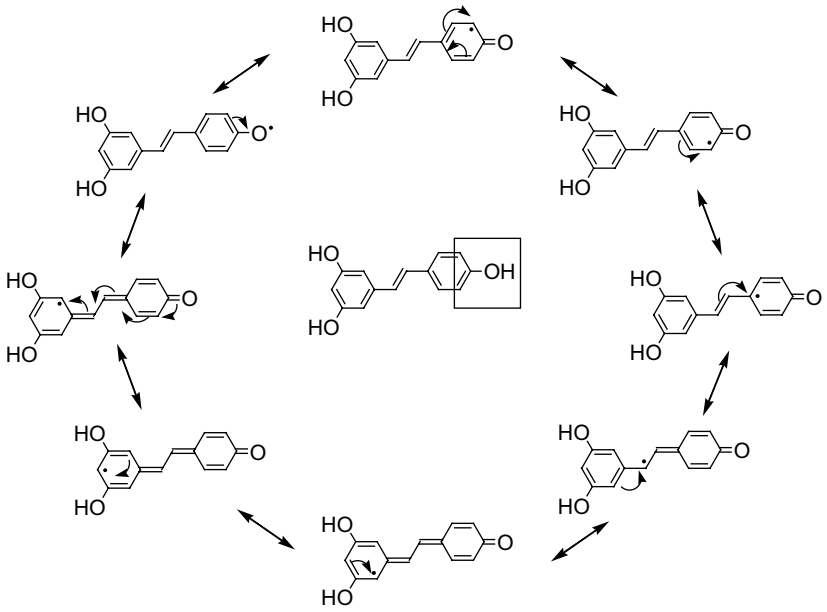

Fig. 3. The resonance structures of semiquinone by hydrogen abstraction of the OH in *para* positions.

$$LOO^{\bullet} + PhOH \rightarrow LOOH + PhO^{\bullet} \quad (4)$$

3.4. Stabilization energies (ΔE_{iso})

The stabilization energies (ΔE_{iso}) of resveratrol and related derivatives are compared with stilbene. The ΔE_{iso} values are shown in Table 1. According to these values it is possible to establish the following relative stability for the involved groups in pharmacophore antioxidant of the resveratrol.

Determination of stabilization energy is frequently used as a simple method to predict the antioxidants' ability to trap free radicals or scavenging effects of phenolic derivatives [19,20,22–26]. This study provides further evidence for the importance of 4-hydroxystilbene and its *ortho*-hydroxylation in the stabilization of radical species by electron or hydrogen abstraction. The results demonstrated a clear classification among different subclasses. In the presence of an additional hydroxyl ΔE_{iso} increased for compounds **15**–**17** to −14.85, −20.95, and −21.18 kcal mol^{-1}, respectively, because of the fact that more oxygen atoms of the phenolic hydroxyl groups can be π-type electrons donated to stabilize the semiquinone free radical.

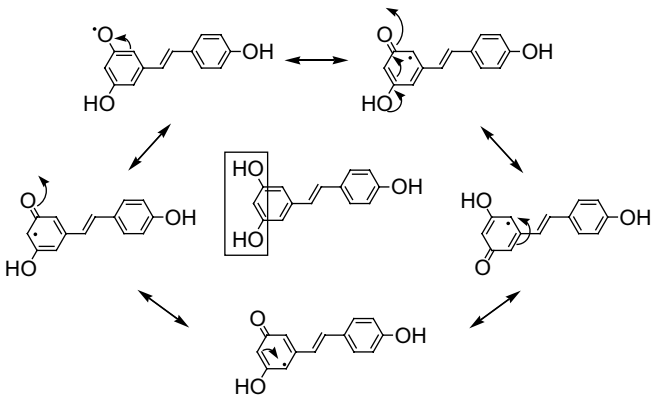

Fig. 4. The resonance structures of semiquinone by hydrogen abstraction of the OH in *meta* positions.

All derivatives hydroxylated in *para* position were less active than former group of compounds. In fact, they were still as active as resveratrol. However, the presence of hydroxyl in *para* position showed ΔE_{iso} for compounds **1**, **2**, **5**, and **13** to be −5.84, −5.24, −5.34, and −6.10 kcal mol^{-1}, respectively.

Nevertheless, the absence of hydroxyl group in *para* position, the double bond, and phenyl group decreased ΔE_{iso}. These compounds showed lowest value of ΔE_{iso} in scale of −3.38 to 1.35 kcal mol^{-1}. Therefore, the alkenes and phenyl ring may stabilize the radical formed during oxidation, by extension of the conjugation via resonance effect, contributing to the decrease of ΔE_{iso}. These results showed that the hydroxyl group in *meta* position has the same contribution that alkene, styrene and phenyl groups in the resveratrol structure has. Consequently, 4-hydroxystilbene showed more contribution in the stabilization of the hydrogen or electron abstraction of resveratrol and its derivatives. The relatively lowest stability found for the hydroxyl hemolytic cleavage in *meta* position may be explained by the fact that the unpaired electron cannot be delocalized in the B-ring.

3.5. Spin density and unpaired electron distribution of radicals

The resonance structures of semiquinone free radicals obtained by hydrogen abstraction of the OH can be observed by spin densities' distribution for the resveratrol and related derivatives. Fig. 5 shows the spin densities' distribution of the semiquinone free radicals of the resveratrol and related derivatives. All structures of spin densities' distribution corresponded to the lowest BDE_{OH} values.

The calculated spin density to initial electron abstraction at the resveratrol (**1**) and related derivatives (**2** and **5**) shows main contribution to be from the phenoxyl group in *para* position (0.32), global contribution from the B-ring (0.94), C_7 carbon atoms at the double bond (0.32), and global contribution from the A-ring (0.26–0.28). The contribution from O_3 and O_5 phenolic oxygens is either almost an order of smaller magnitude or absence of contribution. These compounds are good antioxidants.

Moreover, its related derivatives (**3**, **4**, and **14**) show an increase in contribution from the phenoxyl (0.41–0.43), a smaller contribution from B-ring (0.04), an increased contribution from A-ring

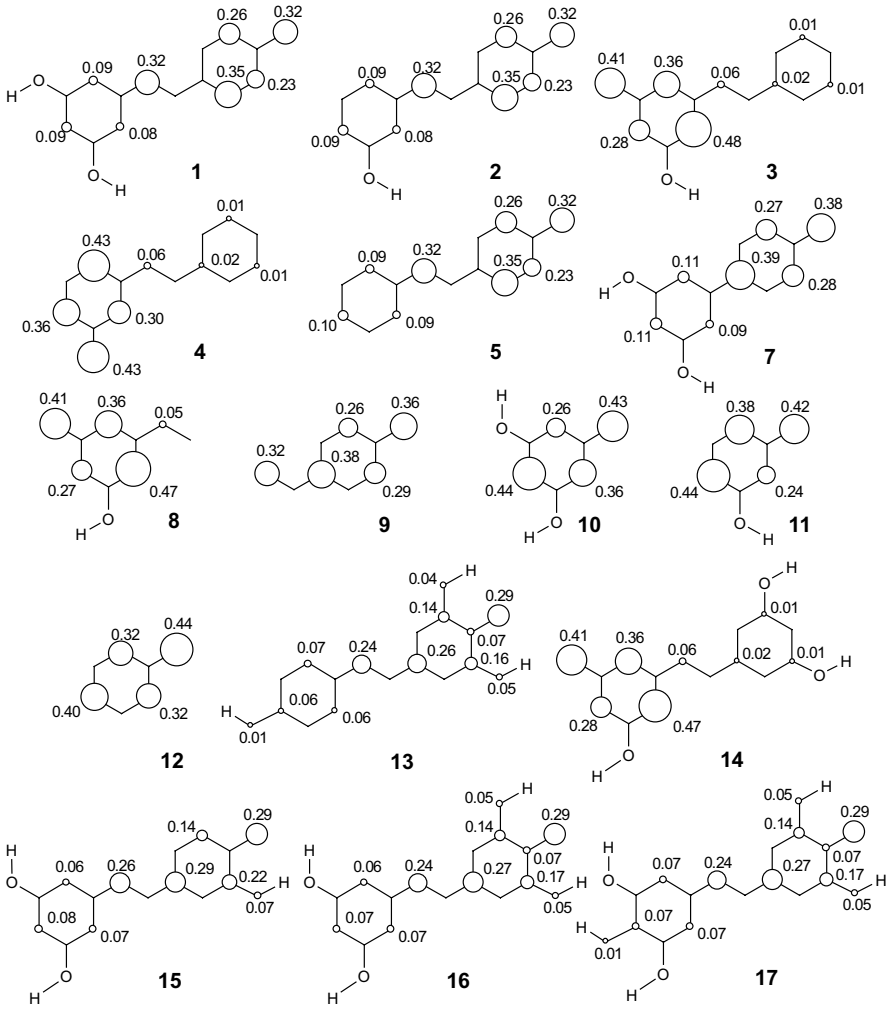

Fig. 5. Spin densities in the semiquinone of resveratrol derivatives.

(1.09–1.12), and C_7 carbon atoms at the double bond (0.06). These compounds are not good antioxidants.

Nevertheless, its related derivatives (**13**, **15**–**17**) show a decrease in contribution from the phenoxyl (0.29), a decreased contribution from B-ring (0.63–0.65), an increased contribution from A-ring (0.19–0.21), and an increased contribution of C_7 carbon atoms at the double bond (0.24–0.26). These compounds showed an additional contribution from the oxygen, *ortho* related to phenoxyl (0.04–0.07). These compounds are excellent antioxidants.

Therefore, the lowest localization of the unpaired electron on the phenoxyl and global contribution of B-ring, together with highest localization of the unpaired electron on the double bond and global contribution of A-ring explain the highest stability of derivatives with additional phenol in *para* position. Others compounds are almost an order of magnitude such as resveratrol derivatives with phenol in *meta* position.

3.6. Identification of antioxidant pharmacophore

The prevalent contributions of HOMO, IP, BDE_{OH}, ΔE_{iso}, and spin densities of the 4-hydroxystilbene are determinants for the biggest stable free radical and more resonance structures. The results showed that the π-type electron system of 4-hydroxystilbene is the majorly responsible pharmacophore antioxidant for resveratrol. Our results for the electron abstraction are in accordance with the results obtained by Cao and co-workers [19] for the hydrogen abstraction. Moreover, Cai and co-workers [27] showed that these stilbene derivatives are effective antioxidants against both AAPH- and iron-induced peroxidation of rat liver microsomes with an activity sequence of **1** > **5** > **3**. These results are expected to search for a possible way to develop resveratrol analogues with a better antioxidant activity and 4-hydroxystilbene will be in the drug's design.

In fact, an additional hydroxylation at 3′ and 5′ positions of 4-hydroxystilbene (**13**, **15**–**17**) increased antioxidant activity. Murias and co-workers [28] reported that resveratrol derivatives are more active than resveratrol in DDPH model. These derivatives were over 6600–3300-fold more active than resveratrol. Nevertheless, the absence of hydroxyl group in *para* position decreased the antioxidant activity, such as compound **14**. Therefore, we clarify the possible link between antioxidant activity of resveratrol and 4-hydroxystilbene, as its pharmacophore antioxidant.

4. Conclusion

Our results manifest that resveratrol is a potential antioxidant because its cation or semiquinone free radicals have several resonance structures in which the unpaired electron is mainly distributed on the 4-hydroxystilbene. The hydroxyl group in *para* position and the double bond of resveratrol contribute to the decrease of HOMO, PI and BDE_{OH} values, and to the increase of ΔE_{iso} value, than the hydroxyl groups in *meta* positions. The electron abstraction in

para position is more favored than in *meta* positions. The prevalent spin density contribution of 4-hydroxystilbene is the determinant for the highest stability free radical and more resonance structures. Additional hydroxylation at 3′ and 5′ positions increased antioxidant activity. The antioxidant activity of resveratrol is related to the stabilization energy of 4-hydroxystilbene in resveratrol hydroxylated derivatives.

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