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Reactivity Indexes and O-H Bond Dissociation Energies of a Large Series of Polyphenols: Implications for their Free Radical Scavenging Activity

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To Professor José Luis Gázquez Mateos for being a great example and a constant motivation. We sincerely thank him for sharing his kindness and knowledge with all of us.

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Abstract. Several chemical descriptors have been evaluated for thirty polyphenols within the frame of the Density Functional Theory (DFT). They were used to investigate the donor and accepting electron capabilities, the fractional charge transfer feasibility, and the H transfer ability of these compounds. It was found that for deactivating free radicals Myricetin has the highest activity via H transfer, while Galangin and piceatannol are the best scavengers through the single electron transfer mechanism for nucleophilic and electrophilic free radicals, respectively.
Key words: Electrodonating Power, Electroaccepting Power, Ionization Energies, Electron Affinities, Bond Dissociation Energies, Antioxidant.

Resumen. Varios descriptores químicos fueron evaluados para treinta polifenoles, dentro del marco de la Teoría de Funcionales de la Densidad. Fueron utilizados para investigar la capacidad electrodonadora y electroaceptora, la facilidad de donación parcial de carga y la transferabilidad de H de estos compuestos. Se encontró que la miricetina presenta la mayor actividad vía transferencia de H, mientras que la galangina y el piceatanol son los mejores desactivantes vía transferencia electrónica simple para radicales nucleofílicos y electrofílicos, respectivamente.
Palabras clave: Poder electrodonador, poder electroaceptor, energía de ionization, afinidad electrónica, energías de disociación de enlace, antioxidantes.

Introduction

Oxidative stress (OS) is a chemical stress that can be defined as the imbalance between biochemical processes leading to the production of free radicals and those responsible for their removal [1]. It has attracted great deal of attention in the last decades due to the increasing evidence supporting its role in the development of a large number of health disorders such as cancer [2], cardiovascular disorders [3], atherosclerosis [4], and Alzheimer's disease [5]. Since OS involves reactions between free radicals and molecules of high biological importance such as DNA and proteins, the study of compounds with free radical scavenging activity becomes an important area of research aiming to prevent OS and the consequent molecular damage.

Polyphenols are consumed in human diet in a wide variety of foods and beverages, such as: fruits, vegetables, wine, coffee, tea, etc. [6]. They are ubiquitous and versatile substances, which have been identified to play multiple biological roles, including cardioprotective [7] effects, and anti-inflammatory [8], antimicrobial and antiviral [9] activities. They are also used to prevent and treat cancer [10] and neurodegenerative diseases [11] and to prevent skin damage [12] and osteoporosis [13]. They are also reported to have excellent antioxidant activity [14], which is the focus of the present study. This particular activity is so important that more than 7500 scientific reports have been devoted to it in the last two decades [15]. However, to our best knowledge there is no previous systematic study on a large series of polyphenols testing chemical descriptors as indicators of their potential antioxidant activity.

It has been demonstrated that the antioxidant activity of polyphenols takes place mainly by H transfer (HT) from the phenolic sites [16-25] and by single electron transfer (SET) from the phenol to the oxidant [21, 24, 25-27]. Therefore O-H bond dissociation energies (BDE) and ionization energies (IE) are relevant to the evaluation of the antioxidant activity of these compounds. Accordingly it is the main goal of the present work to evaluate the O-H BDEs and the IEs of a series of 30 polyphenols with different structural features. BDE have been analyzed for the homolytic bond cleavage since proton transfers are not studied in this work. In addition, it has been proven that in the particular case of the superoxide radical anion ($O_2^{\bullet-}$) the electron transfer actually takes place from this species to the free radical scavenger [28]. The same mechanism was also proposed for the NO radical [29]. Therefore to analyze this particular reaction path we have also studied the electron affinity (EA).

In addition Gázquez *et al.* [30]. have recently proposed the electroaccepting power (ϖ^+) and the electrodonating power (ϖ^-) indexes. They are ideal for describing the propensity of a given chemical species to accept or donate fractional amounts of charge. They are expected to show a similar behavior to that of the first ionization potential and the electron affinity, respectively. However, while *IE* and *EA* measure the capability of a chemical system to donate or accept one electron, ϖ^+ and ϖ^- measure the capability of a chemical system to donate or to accept a small fractional amount of charge [31]. Polyphenols have polar groups and consequently they can form weak bonded complexes with the molecules in their environment. In physiological media there are abundant compounds which can interact in this way with polyphenols. Since this kind of interactions usually takes place by fractional charge transfer we have used ϖ^+ and ϖ^- to evaluate the propensity of polyphenols

to participate in such chemical interactions driven by donor-acceptor processes.

Computational Details

All the electronic calculations have been carried out with the package of programs Gaussian 09 [32], using the PBE0 functional [33] and the 6-31+G(d,p) basis set. This functional has been chosen for being parameter-free. Full geometry optimizations, without any symmetry constraints, and frequency calculations were performed for all the species and local minima were identified by the absence of imaginary frequencies.

Vertical ionization energies (*IE*) and electron affinities (*EA*) were calculated as:

$$IE = E_{N-1}(g_N) - E_N(g_N) \quad (1)$$

$$EA = E_N(g_N) - E_{N+1}(g_N) \quad (2)$$

Where $E_N(g_N)$ is the energy of the *N*-electron system calculated at the geometry g_N and $E_{N-1}(g_N)$ and $E_{N+1}(g_N)$ are the energies of the $(N-1)$ and $(N+1)$ electron systems, calculated also at the g_N geometry.

The electroaccepting power (ϖ^+) and the electrodonating power (ϖ^-) indices have been calculated as proposed by Gázquez *et al.* [30]:

$$\overline{\omega}^+ = \frac{(IE + 3EA)^2}{16(IE - EA)} \quad (3)$$

and

$$\overline{\omega}^- = \frac{(3IE + EA)^2}{16(IE - EA)} \quad (4)$$

The O-H bond dissociation energies (BDE) have been computed as the energy evolution associated with the homolytic rupture of the OH bond:

$$R - OH \rightarrow R - O^{\bullet} + H^{\bullet}$$

BDE values have been calculated for all the OH moieties in the studied polyphenols, and the most favored process has been identified. They are reported in terms of Gibbs free energies (ΔG), at 298.15 K, to take into account the entropy changes.

Results and Discussion

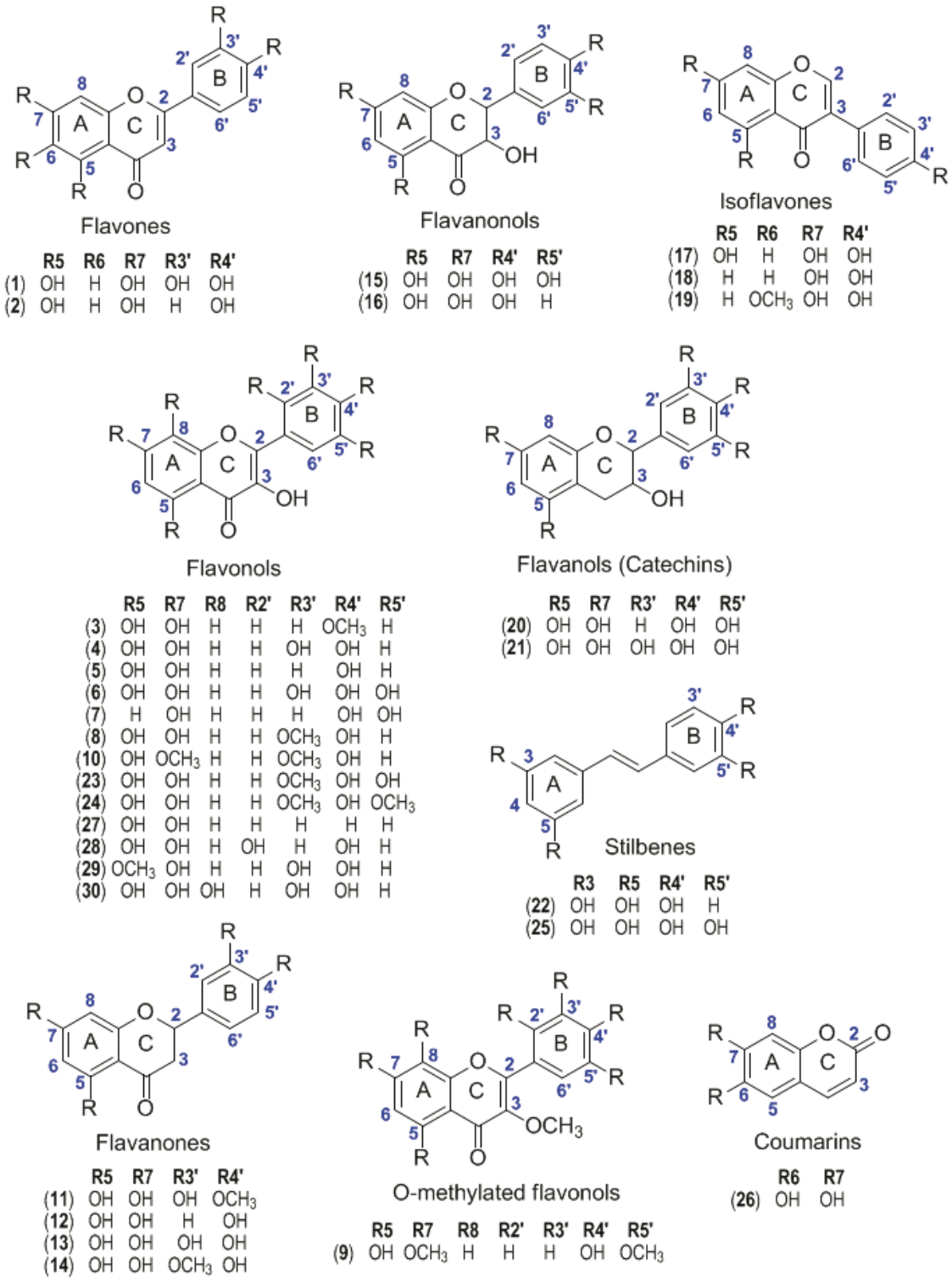
The polyphenols studied in this work are presented in Figure 1, and their names associated with each acronym are provided in Table 1. These polyphenols have different numbers of OH groups, varying from 2 to 6, and according to their structures they belong to different families. In the studied set of polyphenols there are 13 flavonols, 4 flavanones, 3 isoflavones, 2 flavones, 2 flavanonols, 2 flavanols, 2 stilbenes, 1 coumarin and 1 O-methylated flavonol.

Table 1. Name and acronyms of the polyphenols studied in this work.

Acronym	Name	Acronym	Name
1	Luteolin	**16**	Aromadedrin
2	Apigenin	**17**	Genistein
3	Kaempferide	**18**	Daidzein
4	Quercetin	**19**	Glycitein
5	Kaempferol	**20**	Catechin
6	Myricetin	**21**	Gallocatechin
7	Fisetin	**22**	Resveratrol
8	Isorhamnetin	**23**	Laricitrin
9	Pachypodol	**24**	Syringetin
10	Rhamnazin	**25**	Piceatannol
11	Hesperetin	**26**	Aesculetin
12	Naringenin	**27**	Galangin
13	Eriodictyol	**28**	Morin
14	Homoeriodictyol	**29**	Azaleatin
15	Taxifolin	**30**	Gossypetin

The O-H bond dissociation energies (BDE) have been calculated for every O-H site, and their values are reported in Table 2. The lowest BDE value for each compound has been highlighted in bold letters. As the values in this table show, for those families that contain O-H sites in the B ring the lowest BDE always corresponds to one of these sites, regardless of the other structural features, with the exception of flavonols. This strongly supports the hypothesis that for these families the hydroxyl groups in the B ring are responsible for the antioxidant activity of polyphenols, through the H transfer mechanism (HT). For flavonols, on the other hand, site 3 is the one that most frequently corresponds to the lowest value of BDE. The other families with an OH group in site 3 are flavanonols and flavanols. However for them the BDE of this OH group is higher than those of the OH groups in the B ring. The main difference between these two families and flavonols is that for the latter there is a double bond between C2 and C3. Therefore it seems that this structural feature is mandatory for the increased reactivity of site 3.

For the studied flavones, the lowest BDE corresponds to the OH in site 4', even for apigenin (**2**) which has two OH groups in ring A and only one of them in ring B. In addition the presence of a second OH in the B ring decreases the BDE value. Therefore the smallest BDE for **1** is significantly lower (~9 kcal/mol) than the smallest BDE for **2**. A similar behavior was found for isoflavones, i.e the OH in site 4' has the lowest BDE, even for genistein (**17**), which has two OH in the ring A and only one in the ring B. For this family all the smallest BDE are very close, since for all of them there is only one OH group in the B ring. In addition these values are also close to that of **2**, suggesting that the location of the B ring (in sites 2 or 3) does not alter the HT feasibility. Therefore the antioxidant activity of flavones and isoflavones, through this mechanism,



	R5	R6	R7	R3'	R4'
(1)	OH	H	OH	OH	OH
(2)	OH	H	OH	H	OH

	R5	R7	R4'	R5'
(15)	OH	OH	OH	OH
(16)	OH	OH	OH	H

	R5	R6	R7	R4'
(17)	OH	H	OH	OH
(18)	H	H	OH	OH
(19)	H	OCH_3	OH	OH

	R5	R7	R8	R2'	R3'	R4'	R5'
(3)	OH	OH	H	H	H	OCH_3	H
(4)	OH	OH	H	H	OH	OH	H
(5)	OH	OH	H	H	H	OH	H
(6)	OH	OH	H	H	OH	OH	OH
(7)	H	OH	H	H	H	OH	OH
(8)	OH	OH	H	H	OCH_3	OH	H
(10)	OH	OCH_3	H	H	OCH_3	OH	H
(23)	OH	OH	H	H	OCH_3	OH	OH
(24)	OH	OH	H	H	OCH_3	OH	OCH_3
(27)	OH	OH	H	H	H	H	H
(28)	OH	OH	H	OH	H	OH	H
(29)	OCH_3	OH	H	H	OH	OH	H
(30)	OH	OH	OH	H	OH	OH	H

	R5	R7	R3'	R4'	R5'
(20)	OH	OH	H	OH	OH
(21)	OH	OH	OH	OH	OH

	R3	R5	R4'	R5'
(22)	OH	OH	OH	H
(25)	OH	OH	OH	OH

	R5	R7	R3'	R4'
(11)	OH	OH	OH	OCH_3
(12)	OH	OH	H	OH
(13)	OH	OH	OH	OH
(14)	OH	OH	OCH_3	OH

	R5	R7	R8	R2'	R3'	R4'	R5'
(9)	OH	OCH_3	H	H	H	OH	OCH_3

	R6	R7
(26)	OH	OH

Fig. 1. Polyphenols studied in this work.

is expected to be very similar provided that they have the same number of OH groups in the B ring and that they are in the same sites. The different substitutions in the A ring were found to have only minor effects on this activity.

For flavanonols and flavanones which have a single bond between carbons 2 and 3 and a carbonyl group, it was also found that the smallest BDE decreases with the presence of a second OH in the B ring. However, in these cases, the BDE of the OH groups in sites 4' and 5' are very close and within the uncertainty of the calculations. This is a logical finding since the conjugation is broken due to the single bond, and therefore the major effects are due to the neighboring groups. The lower

Table 2. O-H bond dissociation energies (BDE, kcal/mol) for the different phenolic sites.

family	phenol	site	BDE	family	phenol	site	BDE
flavonols	3	**3**	**73.83**	flavones	1	5	99.65
		5	88.21			7	80.55
		7	79.56			3’	68.49
	4	**3**	**64.99**			**4’**	**66.95**
		5	99.58		2	5	92.25
		7	80.32			7	80.52
		3’	69.66			**4’**	**75.61**
		4’	67.70	flavanones	11	5	77.13
	5	**3**	**64.62**			7	78.67
		5	91.03			**3’**	**69.65**
		7	80.34		12	5	77.01
		4’	75.46			7	78.58
	6	3	66.48			**4’**	**75.28**
		5	90.95		13	5	77.15
		7	80.42			7	78.65
		3’	67.23			3’	67.76
		4’	**58.65**			**4’**	**67.08**
		5’	66.47		14	5	77.00
	7	**3**	**65.30**			7	78.61
		7	77.80			**4’**	**75.07**
		4’	69.24	flavanonols	15	3	96.35
		5’	67.11			5	89.29
	8	**3**	**72.92**			7	82.21
		5	88.03			4’	67.34
		7	79.63			**5’**	**67.12**
		4’	74.40		16	3	96.45
	10	**3**	**65.23**			5	89.39
		5	99.63			7	82.16
		4’	75.58			**4’**	**75.68**
	23	3	74.30	flavanols	20	3	90.77
		5	88.41			5	72.66
		7	79.50			7	74.03
		4’	72.44			4’	67.10
		5’	**66.89**			**5’**	**66.46**
	24	**3**	**63.83**		21	3	91.14
		5	99.54			5	74.38
		7	80.11			7	74.62
		4’	70.58			3’	67.14
	27	**3**	**66.10**			**4’**	**63.72**
		5	91.00			5’	67.25
		7	80.58	isoflavones	17	5	91.50
	28	**3**	**68.06**			7	81.21
		5	90.72			**4’**	**74.55**
		7	80.06		18	7	78.44
		2’	75.86			**4’**	**74.02**
		4’	76.24		19	7	78.36
	29	3	74.46			**4’**	**73.74**
		7	78.54	stilbenes	22	3	76.57
		3’	68.68			5	74.76
		4’	**66.06**			**4’**	**70.31**
	30	3	65.41		25	3	76.75
		5	84.13			5	74.96
		7	73.40			4’	66.27
		8	**65.05**			**5’**	**62.88**
		3’	69.74	coumarins	26	**6**	**66.61**
		4’	67.81			7	67.07
O-methylated flavonols	9	5	99.39				
		4’	**74.65**				

reactivity of ring A, with respect to ring B, seems to be caused by the electron-withdrawing power of the carbonyl group. This is confirmed by analyzing the BDE values for flavanols, which also present a single bond between carbons 2 and 3 but have no carbonyl group in ring C. For this family the BDE of the O-H group in site 5 is about 10 kcal/mol lower than for flavanonols.

For the stilbenes the BDE of piceatannol (**25**) is the smallest one. It is even lower than that of resveratrol (**22**), which suggests that **25** should be better antioxidant trough HT, despite of the fact that it has attracted less attention than **22**. For **25** the higher reactivity of ring B (BDEs about 8 kcal/mol lower) is explained by the fact that in this ring the two OH groups are in *ortho* position, while in ring A they are in *meta* position. Since the OH group activate *ortho* and *para* sites, the presence of the second OH in the B ring causes a lower BDE. In addition, the vicinity of the two OH groups in ring B allows additional stabilization due to H bonding interactions. For the studied coumarin (aesculetin, **26**) the higher reactivity of the OH in site 6 can be explained by the *para* activating effect of the ether group.

Since flavonols are the most abundant dietary polyphenols we have studied a larger set of these compounds. As mentioned above for most of them the most reactive OH is that in site 3. The exceptions are myricetin (**6**), laricitrin (**23**), azaleatin (**29**), and gossypetin (**30**). For the latter, site 8 was found to be the most reactive one. Among the studied flavonols this is the only one with an OH group in this site, which is activated by the neighbor OH, which activates *ortho* and *para* sites, and also provides extra stabilization by H bond interactions. For **29** the smallest BDE correspond to the OH in site 4', and for **23** to the OH in site 5'. These variations seem to be caused by the presence of the OCH_3 group. Myricetin, is the only studied polyphenol with three neighbor OH groups in ring B. This makes myricetin particularly reactive though HT from site 4', since it has two OH activating and forming H bonds. This structural feature causes **6** to have the lowest BDE in the studied series, with its smallest value equal to 58.65 kcal/mol. This finding strongly supports that myricetin should be exceptionally good for H transfer.

To facilitate comparisons among all the studied polyphenols, the whole data will be analyzed in terms of relative magnitudes. Since quercetin (**4**) is probably the most studied of the series, and its antioxidant activity has been abundantly demonstrated,[34] we have chosen this compound as reference for the analysis of the other studied compounds. Accordingly, the relative BDEs have been calculated as:

$$\Delta BDE = BDE_{(i)} - BDE_{(4)} \quad (5)$$

where ΔBDE represents the BDE of the polyphenol i ($BDE_{(i)}$), with respect to that of quercetin ($BDE_{(4)}$).

As Figure 2 shows myricetin (**6**), piceatannol (**25**), gallocatechin (**21**), syringetin (**24**) and kaempferol (**5**) have lower BDE than quercetin, suggesting that all of them should be better free radical scavengers, through the HT mechanism. However the difference between **5** and **4** is rather small. Therefore the

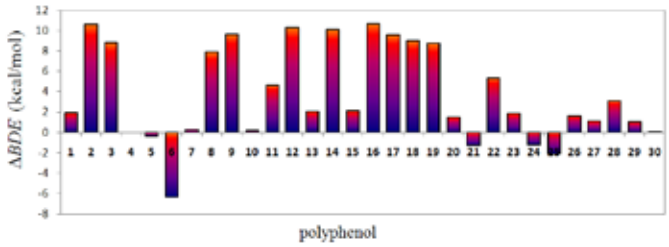


Fig. 2. O-H BDE of the studied phenols, relative to that of quercetin (**4**), it has been constructed using the smallest BDE value for each polyphenol.

order of HT reactivity is predicted to be: myricetin >> piceatannol > gallocatechin ≈ syringetin > kaempferol ≈ quercetin. On the other hand polyphenols **2**, **3**, **8**, **9**, **11**, **12**, **14**, **16**, **17**, **18**, **19** and **22** are expected to be significantly less reactive than quercetin by the HT mechanism. Due to the uncertainties inherent to any calculation, the BDEs of **7**, **10**, and **30** can be considered equivalent to that of **4**.

The chemical descriptors used in this work to investigate the fractional and full electrodonating and electroaccepting capabilities of the studied phenols are reported in Table 3. As mentioned in the introduction, the descriptors relevant to fractional charge transfers are the electroaccepting power (ϖ^+) and the electrodonating power (ϖ^-) indexes. Since charge acceptance processes stabilize the system, larger values of ϖ^+ imply a larger capability to accept electrons. Charge donating processes, on the other hand, destabilize the system and therefore smaller values of ϖ^- indicate a larger capability to donate electrons [31]. In order to facilitate comparisons, the relative values of these indexes, with respect to quercetin have been calculated in a similar way that it was performed for the bond dissociation energies:

$$\Delta\omega^+ = \omega^+_{(i)} - \omega^+_{(4)} \quad (6)$$

$$\Delta\omega^- = \omega^-_{(i)} - \omega^-_{(4)} \quad (7)$$

The values of $\Delta\varpi^-$ and $\Delta\varpi^+$ are plotted in Figures 3 and 4. Regarding the capability of donating fractional amounts of charge, those of polyphenols **3**, **5**, **8**, **9**, **15**, **23**, **29**, and **30** were found to be similar to that of quercetin. Compounds **1**, **2**, **6**, **10**, **16**, **26**, and **27** have values of ϖ^- higher than that of **4**, suggesting that their electrodonating capability is inferior to that of the reference compound. For the polyphenols with values of ϖ^- lower than that of **4** (Figure 3), the order of their electrodonating capability was found to be: **21** > **20** >> **22** > **14** > **13** > **12** > **11** > **25** > **19** > **18** > **28** > **17** > **7** > **24**. These results indicate that, among the studied compounds, gallocatechin (**21**) and catechin (**20**) are particularly good for interactions with electrophilic agents. They are both flavanols, which suggests that this particular family of polyphenols might be involved in stronger weak bonded complexes with electrophiles than the other families studied in the present work. With respect to the

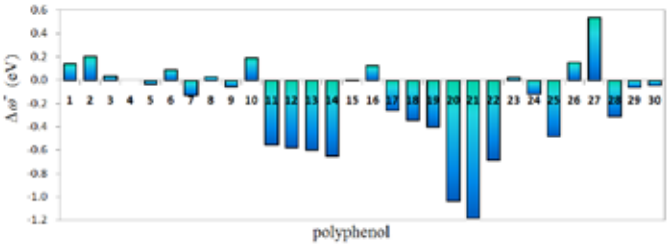


Fig. 3. Electrodonanting power (ϖ^-) of the studied phenols, relative to that of **4** (quercetin).

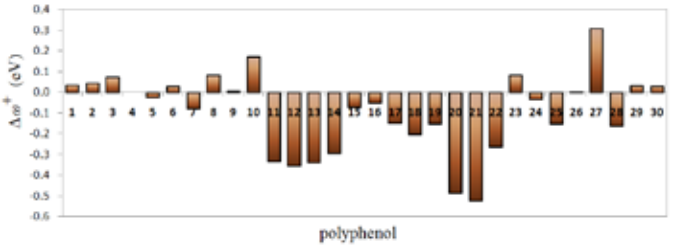


Fig. 4. Electroaccepting power (ϖ^+) of the studied phenols, relative to that of **4** (quercetin).

capability of accepting fractional amounts of charge, most of the studied polyphenols were found to have lower values of ϖ^+ than quercetin (Figure 4), i.e. they are poorer electron acceptors than the reference compound. The electroaccepting powers of polyphenols **1**, **2**, **5**, **6**, **9**, **24**, **26**, **29**, and **30** were found to be similar to that of quercetin. Only a few polyphenols were found to have values of ϖ^+ higher than that of **4**. The order of their electroaccepting capability was found to be: **27** >> **10** > **8** > **23** ≈ **3**. These results indicate that gallangin (**27**) is particularly good for interactions with nucleophilic agents, and therefore it is expected to complexate with nucleophiles in a stronger way than the other compounds studied in the present work.

Relative values of *IE* and *EA*, with respect to quercetin (**4**) have been calculated as:

$$\Delta IE = IE_{(i)} - IE_{(4)} \quad (8)$$

$$\Delta EA = EA_{(i)} - EA_{(4)} \quad (9)$$

and the results are shown in Figures 5 and 6, respectively. The IE values of **5**, **7**, **17**, **20**, **27**, and **28** were found to be very similar to that of **4**. Thus they are predicted to be as efficient as the reference compound to scavenge free radicals through the SET mechanism, by donating one electron. The sub-set of polyphenols that are predicted to be less efficient than quercetin, through this process, are: **1**, **2**, **6**, **11**, **12**, **13**, **15**, **16**, **18**, and **26**. The order of reactivity for those compounds that are predicted to donate one electron to free radicals easier than **4** is: **25** > **22** > **23** ≈ **19** ≈ **29** ≈ **8** ≈ **10** > **30** ≈ **3** (Figure 5) It seems important to notice that the ability to donate fractional or full charge is not the same within this series. Therefore those

Table 3. Chemical descriptors: ionization energies (IE, eV), electron affinities (EA, eV), electroaccepting power (ϖ^+, eV), and electrodonating power (ϖ^-, eV).

	IE	EA	ϖ^-	ϖ^+
1	7.706	0.619	4.969	0.807
2	7.796	0.629	5.030	0.817
3	7.324	0.710	4.861	0.844
4	7.527	0.580	4.826	0.772
5	7.561	0.531	4.791	0.745
6	7.610	0.619	4.916	0.801
7	7.568	0.438	4.695	0.692
8	7.274	0.729	4.856	0.855
9	7.375	0.605	4.770	0.780
10	7.290	0.856	5.016	0.944
11	7.777	–0.114	4.270	0.438
12	7.840	–0.178	4.247	0.416
13	7.712	–0.121	4.227	0.431
14	7.354	0.041	4.176	0.478
15	7.838	0.421	4.827	0.698
16	8.009	0.446	4.950	0.722
17	7.584	0.307	4.567	0.621
18	7.620	0.202	4.481	0.570
19	7.263	0.341	4.422	0.620
20	7.493	–0.487	3.789	0.285
21	7.372	–0.585	3.641	0.248
22	7.121	0.142	4.141	0.510
23	7.256	0.730	4.847	0.854
24	7.400	0.534	4.705	0.738
25	7.086	0.361	4.343	0.620
26	7.859	0.552	4.980	0.774
27	7.542	1.022	5.360	1.079
28	7.513	0.295	4.514	0.611
29	7.265	0.652	4.762	0.803
30	7.319	0.641	4.780	0.800

compounds forming the stronger complexes are not necessarily those more prompt to donate one electron, and therefore for deactivating free radicals this way. Through this mechanism piceatannol (**25**) and resveratrol (**22**) are predicted to be the most active ones. This suggests that stilbenes are particularly good for scavenging free radicals by SET, when the transfer takes place from the antioxidant to the radical, which is the most common case. Additionally, the number of OH in ring B of stilbenes seems to potentiate this activity.

Regarding the SET mechanism in the opposite direction, i.e. with the electron transfer from the radical to the antioxidant, the proper chemical descriptor is the *EA*. As shown in Figure 6, most of the studied polyphenols have lower values of *EA* than quercetin, i.e. they have lower activity than the reference compound to deactivate free radicals that would be involved

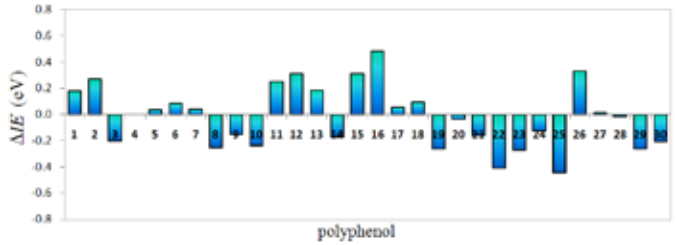


Fig. 5. Ionization energies (*IE*) of the studied phenols, relative to that of **4** (quercetin).

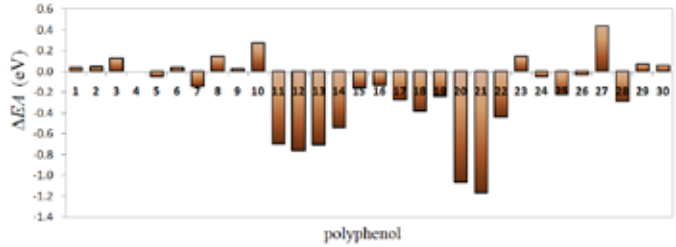


Fig. 6. Electron affinities (*EA*) of the studied phenols, relative to that of **4** (quercetin).

in the SET mechanism by donating one electron. The *EA* of polyphenols **1**, **2**, **5**, **6**, **9**, **24**, **26**, **29**, and **30** were found to be similar to that of quercetin, while only a few were found to have higher *EA* than that of **4**. The order of reactivity of those compounds that are predicted to accept one electron from free radicals easier than **4** was found to be: **27** >> **10** > **23** ≈ **8** ≈ **3**. In the case of *EA* there is a general agreement between the finding trend and that of ϖ^+. According to the presented results for SET reactions with radicals like the superoxide anion ($O_2^{\bullet -}$) gallangin (**27**) is the best free radicals scavenger, followed by rhamnazin (**10**). Moreover, these results also indicate that most polyphenols would not deactivate free radicals by SET from the radicals to the scavenger. According to this finding, compounds **27** and **10** may deserve further investigations.

A map, simultaneously showing the electrodonating capability of the studied compounds and their lowest O-H bond dissociation energies, has been constructed (Figure 7) for all the studied polyphenols relative to quercetin. To obtain a convenient scale we have defined the relative descriptors as:

$$RIE = \frac{IE(i)}{IE(4)} \quad (10)$$

$$RBDE = \frac{BDE(i)}{BDE(4)} \quad (11)$$

IE and BDE values are directly related to the SET (from the polyphenol to the radical) and to the HT mechanisms, respectively. Therefore this map allows easy and direct comparison of the scavenging activity of the studied compounds, when reacting with electrophilic radicals (for example hydroxyl, alkoxyl, and peroxyl radicals). It is important to remember that these are the two main mechanisms involved in the reactions of

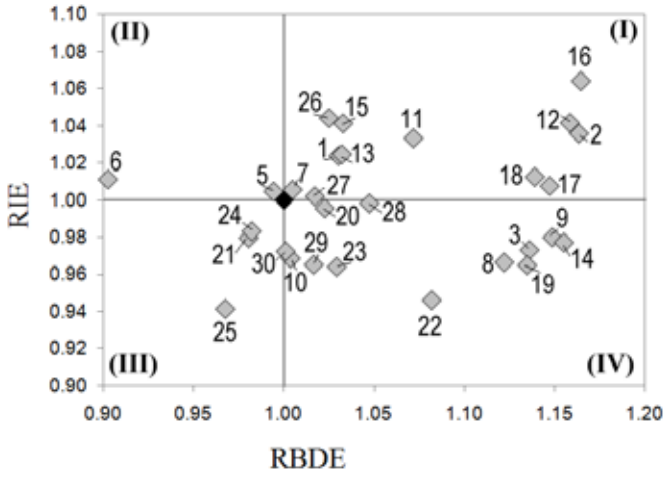


Fig. 7. Ionization energies vs. vs. O-H bond dissociation energies of the studied polyphenols, relative to quercetin.

polyphenols with free radicals, and therefore in their scavenging activity for the above mentioned radicals.

The species located in quadrant III are predicted to be better than quercetin both trough SET (from the polyphenol) and HT, since they have lower IE and lower BDE. The species in quadrant I are worse for both electron and H transfer. Those in quadrant II are better for H transfer but worse for electron transfer, and those in quadrant IV are better for electron transfer but worse for H transfer. Accordingly picceatanol (**25**) has been identified as the best scavenger for electrophilic radicals, followed by gallocatechin (**21**) and syringetin (**24**). It seems to be an important finding since the most damaging, and the most common, free radicals in living organisms are electrophiles and these three polyphenols are not among the most studied polyphenols. Special attention should be paid to piceatannol. This stilbene, which is found in rhubarb, berries, peanuts, sugar cane, wine and the skins of grapes [35]; and is also a metabolite of resveratrol [36], has received less attention than other polyphenols. For example while quercetin and resveratrol appear in the title of more than 3000 articles, according to Scopus, piceatannol only appears 91 times. According to the results from the present work it is expected to be an exceptionally good scavenger of $^{\bullet}$OH, RO$^{\bullet}$, and ROO$^{\bullet}$ radicals.

A second map, simultaneously showing the electron-accepting capability of the studied compounds and the O-H bond dissociation energies is shown in Figure 8. It has been constructed for all the studied polyphenols relative to quercetin using:

$$REA = \frac{EA(i)}{EA(4)} \quad (12)$$

This map is relevant to the reactions with the SET process taking place from the radical to the polyphenol, for example those involving the superoxide radical anion. In this case the compounds in quadrant II are the best scavengers since they have higher EA and lower BDE. Those in quadrant I are better for SET (from the radical) but worse for HT, while those in

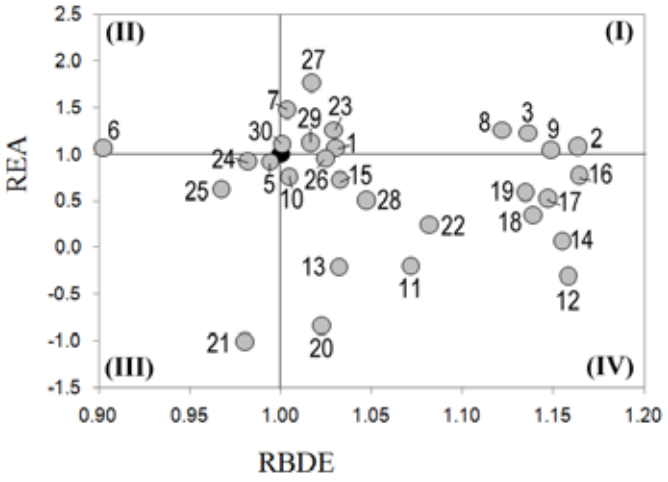


Fig. 8. Electron affinities vs. O-H bond dissociation energies of the studied polyphenols, relative to quercetin.

quadrant III are better for HT but worse for SET. Compounds in quadrant IV are predicted to be worse than quercetin for both mechanisms. To deactivate nucleophilic radicals through SET, galangin (**27**) was found to be the best of the studied polyphenols. However through HT it is not expected to be particularly good. Myricetin (**6**) is the only polyphenol that is predicted to be a better scavenger than quercetin trough both HT and SET mechanisms. Therefore it is identified as the best scavenger, among the studied series, for scavenging $O_2^{\bullet-}$, and other nucleophilic radicals. Moreover, due to its low BDE it is expected to be a very good scavenge, through HT, of any free radical. Its low BDE arises from the pirogallol moiety, since the two OH groups in sites 3' and 5', allow a significant stabilization of the radical formed in site 4' by H bond interactions.

Conclusions

The electrodonating and the electroaccepting capabilities, as well as the O-H bond dissociation energies of thirty polyphenols have been evaluated, at PBE0/6-31+G(d,p) level of theory. The relative reactivity of the studied compounds has been assigned by comparisons with quercetin, due to its well recognized free radical scavenging activity.

For fractional charge transfer processes the electrodonating and the electronaccepting powers were used. Based on these descriptors it was found that among the studied compounds, gallocatechin (**21**) and catechin (**20**) should form particularly strong complexes with electrophilic agents, while gallangin (**27**) is particularly good for interactions with nucleophiles.

O-H bond dissociation energies have been used to estimate the H transfer capability. The order of reactivity, thorough this mechanism of reaction is predicted to be: myricetin (**6**) >> piceatannol (**25**) > gallocatechin (**21**) ≈ syringetin (**24**) > kaempferol (**5**) ≈ quercetin (**4**). The higher capacity of myricetin for H transfer has been rationalized based on the presence of the pyrogallol group.

Ionization energies have been used to investigate the activity of the studied phenols for deactivating electrophilic free radicals through SET (from the phenol to the radical). The order of reactivity is predicted to be: piceatannol (**25**) > resveratrol (**22**) > laricitrin (**23**) ≈ glycitein (**19**) ≈ azaleatin (**29**) ≈ isorhamnetin (**8**) ≈ rhamnazin (**10**) > gossypetin (**30**) ≈ kaempferide (**3**)> quercetin (**4**).

Electron affinities were used to investigate the activity of the studied phenols for deactivating nucleophilic free radicals through SET. The order of reactivity of those compounds that are predicted to accept one electron from free radicals easier than quercetin (**4**) was found to be: gallangin (**27**) >> rhamnazin (**10**) > laricitrin (**23**) ≈ isorhamnetin (**8**) ≈ kaempferide (**3**).

According to all the gathered data picceatanol (**25**) has been identified as the best scavenger for electrophilic radicals ($^{\bullet}$OH, RO$^{\bullet}$, ROO$^{\bullet}$), followed by gallocatechin (**21**) and syringetin (**24**). On the other hand myricetin (**6**) was identified as the best scavenger, among the studied series, for scavenging $O_2^{\bullet-}$, and other nucleophilic radicals.

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