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Original article

A theoretical study of phenolic compounds with antioxidant properties

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Abstract

Quantum chemical calculations at the DFT/B3LYP, HF, and AM1 and PM3 semiempirical levels were employed to calculate a set of molecular properties for 41 phenol compounds with antioxidant activity. The significant molecular descriptors related to the compounds were the vertical ionization potentials (IPvs) and the charge on oxygen atom 7. The IPv has been calculated using Koopman's theorem $\mathrm{IPv} = -\varepsilon_{\mathrm{HOMO(DFT)}}$, $\mathrm{IPv} = -\varepsilon_{\mathrm{HOMO(HF)}}$ and as the difference of energy calculations for the corresponding cation and for the neutral form IPv ($E_{\mathrm{cation}} - E_{\mathrm{neutral}}$) obtained with the DFT/B3LYP method. The best model obtained showed not only the statistical significance but also predictive ability.

Keywords: AM1; PM3; Phenols; Hartree–Fock; DFT; Antioxidant; QSAR

1. Introduction

Antioxidants are of great interest because of their involvement in important biological and industrial processes. In general, compounds with antioxidant activity have been found to possess anticancer, anti-cardiovascular, anti-inflammation and many other activities [1–3].

Many authors have attempted to elucidate the quantitative structure–activity relationships (QSARs) of antioxidants by using different physicochemical parameters like the heat of formation (H_f), the number of hydroxyl groups (OH) and Hammet σ or Brown σ^+, ionization potential (IP), bond dissociation enthalpy (O–H BDE), etc. [4–9]. Recently, Lien et al. [10] have reported on QSAR study of phenols with antioxidant activity by employing descriptors calculated by the semiempirical method AM1. In this study four parameters, namely H_{fr} (heat of formation of phenoxyl), H_{fp} (heat of formation of parent phenols), OH (the number of hydroxyl groups), and LUMO-r (the energy of the lowest unoccupied molecular orbital of radical), were responsible for antioxidant activity. Nevertheless, semiempirical methods approximate certain properties up to a certain level, and it is obvious that variation in LUMO energy values of various congeners is very small, so an important error can be introduced if a low-level quantum method is employed in the calculations.

Therefore, in the present work, four computational methods: density functional (DF), HF (Hartree–Fock), and AM1 and PM3 were employed to explore and determine various electronic descriptors, with better accuracy, to make the necessary improvement in the QSAR models. Vertical ionization potentials (IPvs), electron affinity (EA), electronegativity (χ), hardness (η), softness (S), electrophilic index (ω), partition coefficient (Log P), charges and other properties were obtained for 41 phenolic compounds (see Table 1), which have antioxidant activity [10–12]. The linear regression method [13] has been employed with the aim to obtain a correlation between these descriptors and the antioxidant activity of these compounds. The data obtained will help us to verify which is the best quantum method and which ones are the most adequate properties to explain the antioxidant activity, as well as to verify the validity of Koopman's theorem ($\mathrm{IPv} = -\varepsilon_{\mathrm{HOMO}}$) [14].

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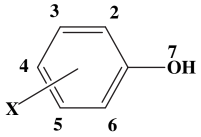
Table 1
Structural skeleton and experimental redox potential [11,12,30]



Compound	Substituent X	E_7 (V)[a]	Compound	Substituent X	E_7 (V)[a]
1	4-NO_2	1.23	**22**	3-OH	0.81
2	3.5-Cl_2	1.15	**23**	2-OCH_3	0.77
3	4-CF_3	1.13	**24**	4-OCH_3	0.73
4	3-NO_2	1.13	**25**	3,4-$(CH_3O)_2$	0.67
5	4-PhCO	1.12	**26**	3,4,5-$(CH_3O)_3$	0.66
6	3-CN	1.11	**27**	Sesamol	0.62
7	4-COOH	1.04	**28**	2-OH 4-COOH	0.60
8	3-CH_3CO	0.98	**29**	2,6-$(CH_3O)_2$	0.58
9	4-H	0.97	**30**	2,3-$(OH)_2$	0.58
10	4-Br	0.96	**31**	2,3-$(OH)_2$ 5-$COOCH_3$	0.56
11	4-Cl	0.94	**32**	3,4-Dihydrocynnamic acid	0.54
12	4-F	0.93	**33**	2-OH	0.53
13	Tyrosine	0.89	**34**	2-OH 4-CH_3	0.52
14	3-OH 4-$COCH_3$	0.89	**35**	4 OH	0.46
15	4-CH_3	0.87	**36**	4-NH_2	0.41
16	3,5-$(CH_3O)_2$	0.85	**37**	4-CN	1.17
17	3-CH_3	0.85	**38**	4-$COCH_3$	1.06
18	3-OH 5-OCH_3	0.84	**39**	4-t-Bu	0.80
19	3,5-$(CH_3)_2$	0.84	**40**	2.6-$(CH_3)_2$	0.77
20	4-Ph	0.84	**41**	2-OCH_3 4-CH_3	0.68
21	2-CH_3	0.82			

[a] From Refs. [11,12,30].

2. Calculation

2.1. Calculated properties

Quantum chemical calculations at the DFT/RB3LYP/6-31G* (restricted B3LYP) [15–17], RHF/6-31G* (restricted Hartree–Fock) [18–20] and AM1 [21] and PM3 [22] semiempirical theory levels, were employed for full optimization of the selected neutral compounds. The geometrical structures of the radicals studied were optimized independently from the neutral molecules prior to the calculation of energies, treated as open shell systems. All calculations were performed by using the Gaussian 03 package of programs [23].

In this work, the more relevant electronic properties for phenolic compounds such as vertical ionization potential (IPv), electron affinities (EA), electronegativity (χ), hardness (η), softness (S), electrophilic index (ω) and charges (Mulliken's charges) on some key atoms were calculated. The calculated vertical ionization potentials (IPvs) and electron affinity (EA) were not corrected for zero-point energy, assuming a negligible error and thus saving computer-time. The IPv was calculated as the energy differences between a radical cation and the respective neutral molecule; IPv$(E_{\text{cation}} - E_{\text{neutral}})_{\text{DFT}}$ and Koopman's theorem (IPv $= -\varepsilon_{\text{HOMO}}$). The EA was computed as the energy differences between a neutral form and the anion molecule; EA $= E_{\text{neutral}} - E_{\text{anion}}$. The Log P (octanol/water partition coefficients), MR (molar refractivity) and topology indices were obtained by using the Chem-3D molecular package [24]. The DFT-based reactivity descriptors were obtained from Eqs. (1)–(4) [25–28].

- Electronegativity (χ):

$$\mu = -\chi \approx -(\text{IP} + \text{EA})/2 \tag{1}$$

- Hardness (η):

$$\eta \approx (\text{IP} - \text{EA})/2 \tag{2}$$

- Softness (S):

$$S = 1/(2\eta) \tag{3}$$

- Electrophilic index (ω):

$$\omega = \mu^2/2\eta \tag{4}$$

2.2. Statistical analysis

Of the 41 compounds studied here five of them were not included in the model; those were used as test set to evaluate the prediction power of the model (molecules **37–41**). Therefore, the regression models and matrix correlation presented in this study were constructed with 36 molecules (compounds **1–36**). The remaining five molecules will be used to evaluate the prediction power of the best model.

The matrix correlation uses the Pearson product moment correlation coefficient to measure the degree of linear relationship between two variables. The correlation coefficient assumes a value between −1 and +1. If one variable tends to increase the other decreases, the correlation coefficient is negative. Conversely, if the two variables tend to increase together the correlation coefficient is positive. We obtained the correlation matrix between redox potential (E_7) values and the respective calculated properties. We considered correlated variables those that possess correlation coefficients above 0.70. The more relevant regression models were selected following three criteria: the correlation coefficient (R), the Fisher ratio values (F) and the standard deviation (s). The MINITAB® Release 14 Software [29] was used in our statistical analyses.

The best equation was also tested for their predictive power using a cross-validation procedure. Cross-validation is a practical and reliable method for testing this significance. In principle, the so-called "leave-one-out" approach consists in developing a number of models with one sample omitted at the time. After developing each model, the omitted data is predicted and the differences between actual and predicted y (E_7) values are calculated. The sum of squares of these differences is computed and finally the performance of the model (its predictive ability) can be given by the PRESS (Predictive Sum of Squares) and S_{PRESS} (standard deviation of cross-validation):

$$\text{PRESS} = \sum_{i=1}^{n} \left(y_i - \widehat{y}_i\right)^2$$

$$S_{\text{PRESS}} = \frac{\sqrt{\text{PRESS}}}{n-k-1} \qquad (5)$$

where y is the experimental value, E_7, $\widehat{y}$ is the predicted value, n is the number of samples used for model building and k is the number of descriptors.

The predictive ability of the model was also quantified in terms of the Q^2 which is defined as:

$$Q^2 = 1.0 - \frac{\sum_{i=1}^{n}(y_i - \widehat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \overline{y}_i)^2} \quad \text{where } \overline{y} = y_{\text{mean}} \qquad (6)$$

2.3. Experimental data

Experimentally determined redox potential at pH 7 (E_7) has been commonly used as a direct measure of the antioxidant activity by several authors [10–12,30]. The compounds used in this study, as well as the experimental redox potential values (E_7) are shown in Table 1.

3. Results and discussion

3.1. Simple linear regression model

We obtained the correlation matrix between antioxidant activity (E_7) values and the respective calculated properties for 36 phenolic compounds. From Table 2 we can see that some variables are correlated to each other (we considered correlated variables those that possess correlation coefficients above

Table 2
Correlation matrix between the selected variables

	$-\varepsilon_{\text{HOMO(AM1)}}$	$-\varepsilon_{\text{HOMO(PM3)}}$	$-\varepsilon_{\text{HOMO(HF)}}$	$-\varepsilon_{\text{HOMO(DFT)}}$	$\text{IPv}(E_{\text{cation}} - E_{\text{neutral}})_{\text{DFT}}$	$\text{O7}_{\text{(DFT)}}$	$\text{O7}_{\text{(HF)}}$	μ	η	S	ω	Log P	E_7
$-\varepsilon_{\text{HOMO(AM1)}}$	1.00												
$-\varepsilon_{\text{HOMO(PM3)}}$	0.98	1.00											
$-\varepsilon_{\text{HOMO(HF)}}$	0.95	0.92	1.00										
$-\varepsilon_{\text{HOMO(DFT)}}$	0.92	0.89	0.98	1.00									
$\text{IPv}(E_{\text{cation}} - E_{\text{neutral}})_{\text{DFT}}$	0.91	0.89	0.94	0.95	1.00								
$\text{O7}_{\text{(DFT)}}$	0.41	0.47	0.47	0.52	0.47	1.00							
$\text{O7}_{\text{(HF)}}$	0.37	0.44	0.43	0.46	0.41	0.99	1.00						
μ	0.85	0.82	0.88	0.91	0.84	0.40	0.33	1.00					
η	−0.31	−0.28	−0.27	−0.31	−0.22	0.01	0.06	−0.67	1.00				
S	0.33	0.31	0.29	0.33	0.24	−0.02	−0.07	0.68	−0.99	1.00			
ω	0.78	0.75	0.79	0.81	0.73	0.32	0.26	0.97	−0.79	0.80	1.00		
Log P	−0.16	−0.14	−0.05	0.03	0.01	0.32	0.30	−0.13	0.35	−0.34	−0.21	1.00	
E_7	0.74	0.75	0.82	0.85	0.81	0.79	0.76	−0.68	−0.04	0.05	0.56	0.31	1.00

Table 3
Values obtained for the vertical ionization potentials $-\varepsilon_{\mathrm{HOMO}}$(AM1, PM3, HF and DFT), IPv($E_{\mathrm{cation}} - E_{\mathrm{neutral}}$)$_{\mathrm{DFT}}$ and experimental redox potential at pH 7(E_7)

Compound	IPv = $-\varepsilon_{\mathrm{HOMO(ev)}}$				IPv($E_{\mathrm{cation}} - E_{\mathrm{neutral}}$)$_{\mathrm{DFT\ (eV)}}$	O7$_{\mathrm{(DFT)}}$	O7$_{\mathrm{(HF)}}$	E_7 (V)
	(AM1)	(PM3)	(HF)	(DFT)				
1	10.07	10.17	9.51	6.92	8.84	−0.63	−0.74	1.23
2	9.54	9.42	9.17	6.63	8.44	−0.63	−0.75	1.15
3	9.79	9.84	9.08	6.52	8.44	−0.63	−0.75	1.13
4	9.95	9.96	9.30	6.78	8.72	−0.63	−0.75	1.13
5	9.38	9.41	8.73	6.27	7.80	−0.63	−0.75	1.12
6	9.58	9.66	9.16	6.68	8.61	−0.64	−0.75	1.11
7	9.61	9.59	8.91	6.42	8.30	−0.63	−0.75	1.04
8	9.38	9.42	8.74	6.30	8.20	−0.64	−0.75	0.98
9	9.11	9.18	8.41	5.96	8.01	−0.64	−0.76	0.97
10	9.19	9.31	8.51	6.04	7.89	−0.64	−0.75	0.96
11	9.12	9.01	8.58	6.09	7.97	−0.64	−0.75	0.94
12	9.09	9.27	8.51	5.94	7.95	−0.65	−0.76	0.93
13	9.20	9.25	8.48	6.00	7.46	−0.64	−0.76	0.89
14	9.43	9.45	8.66	6.17	7.95	−0.64	−0.75	0.89
15	8.88	8.95	8.14	5.73	7.67	−0.65	−0.76	0.87
16	8.96	9.01	8.14	5.55	7.29	−0.65	−0.76	0.85
17	9.05	9.12	8.33	5.88	7.82	−0.65	−0.76	0.85
18	9.05	9.07	8.28	5.66	7.45	−0.65	−0.76	0.84
19	8.97	9.04	8.23	5.78	7.66	−0.65	−0.76	0.84
20	8.55	8.64	7.82	5.63	7.33	−0.64	−0.76	0.84
21	8.96	9.04	8.25	5.82	7.77	−0.64	−0.76	0.82
22	9.13	9.13	8.31	5.77	7.72	−0.65	−0.76	0.81
23	8.79	9.14	7.97	5.45	7.28	−0.63	−0.74	0.77
24	8.65	8.72	7.85	5.36	7.17	−0.65	−0.76	0.73
25	8.40	8.48	7.90	5.34	6.90	−0.65	−0.76	0.67
26	8.40	8.46	8.00	5.48	6.75	−0.65	−0.76	0.66
27	8.77	8.81	7.90	5.26	7.10	−0.65	−0.76	0.62
28	9.47	9.44	8.59	6.03	7.86	−0.67	−0.78	0.60
29	9.00	9.19	7.85	5.25	6.99	−0.65	−0.76	0.58
30	8.99	8.99	8.12	5.44	7.33	−0.68	−0.79	0.58
31	9.26	9.24	8.44	5.79	7.51	−0.68	−0.79	0.56
32	9.09	9.06	8.20	5.86	7.48	−0.67	−0.79	0.54
33	8.80	8.83	8.17	5.62	7.59	−0.68	−0.79	0.53
34	8.66	8.70	8.02	5.51	7.38	−0.68	−0.79	0.52
35	8.73	8.76	7.93	5.41	7.35	−0.65	−0.76	0.46
36	8.27	8.35	7.50	4.99	6.70	−0.65	−0.77	0.41
37	9.51	9.56	9.08	6.60	8.50	−0.63	−0.74	1.17
38	9.43	9.45	8.78	6.35	8.17	−0.63	−0.75	1.06
39	8.90	9.00	8.14	5.75	7.54	−0.65	−0.76	0.80
40	8.89	8.96	8.15	5.71	7.59	−0.65	−0.77	0.77
41	8.72	8.79	8.12	5.66	7.15	−0.64	−0.75	0.68

0.70). Properties found to have significant correlation coefficients with E_7 are presented in Table 3. According to these results the energies of the highest occupied molecular orbital ($-\varepsilon_{\mathrm{HOMO}}$) calculated at AM1, PM3, HF/6-31G* and B3LYP/6-31G* levels, respectively, the ionization potentials IPv($E_{\mathrm{cation}-E\mathrm{neutral}}$)$_{\mathrm{DFT}}$ calculated at B3LYP/6-31G* level and the charge on oxygen atom 7 (O7) for neutral molecule are correlated with the antioxidant activity (E_7). The other calculated properties presented low correlation with experimental redox potential. This result indicates that the antioxidant compound can give an electron to the free radical becoming itself a radical cation. Using E_7 as dependent variable and these properties as independent variables the following models were obtained:

$$\begin{gathered}E_7 = -2.67(\pm 0.55) + 0.40(\pm 0.06) - \varepsilon_{\mathrm{HOMO(AM1)}}\\ n = 36,\ R^2 = 0.54,\ s = 0.15,\ F = 51.43,\\ \mathrm{PRESS} = 0.85,\ Q^2 = 0.50,\ S_{\mathrm{PRESS}} = 0.027\end{gathered} \tag{7}$$

$$\begin{gathered}E_7 = -2.87(\pm 0.56) + 0.40(\pm 0.06) - \varepsilon_{\mathrm{HOMO(PM3)}}\\ n = 36,\ R^2 = 0.56,\ s = 0.13,\ F = 43.63,\\ \mathrm{PRESS} = 0.80,\ Q^2 = 0.55,\ S_{\mathrm{PRESS}} = 0.026\end{gathered} \tag{8}$$

$$\begin{gathered}E_7 = -2.41(\pm 0.38) + 0.38(\pm 0.04) - \varepsilon_{\mathrm{HOMO(HF)}}\\ n = 36,\ R^2 = 0.68,\ s = 0.12,\ F = 70.54,\\ \mathrm{PRESS} = 0.59,\ Q^2 = 0.65,\ S_{\mathrm{PRESS}} = 0.022\end{gathered} \tag{9}$$

$$\begin{gathered}E_7 = -1.51(\pm 0.25) + 0.40(\pm 0.04) - \varepsilon_{\mathrm{HOMO(DFT)}}\\ n = 36,\ R^2 = 0.73,\ s = 0.11,\ F = 89.69,\\ \mathrm{PRESS} = 0.50,\ Q^2 = 0.70,\ S_{\mathrm{PRESS}} = 0.021\end{gathered} \tag{10}$$

$$\begin{gathered}E_7 = -1.74(\pm 0.31) + 0.33(\pm 0.04) - \mathrm{IPv}(E_{\mathrm{cation}} - E_{\mathrm{neutral}})_{\mathrm{DFT}}\\ n = 36,\ R^2 = 0.66,\ s = 0.12,\ F = 66.02,\\ \mathrm{PRESS} = 0.62,\ Q^2 = 0.63,\ S_{\mathrm{PRESS}} = 0.023\end{gathered} \tag{11}$$

where n is the number of compounds, R^2 is the square of correlation coefficient, it is a measure of the fit of the regression model, Q^2 is the cross-validation correlation coefficient, F the Fisher test, reflects the ratio of the variance explained by the model and variance due to the error in the model, high values of the F-test indicate the significance of the equation, PRESS (Predictive Sum of Squares) and S_{PRESS} (standard deviation of cross-validation).

In previous equations $-\varepsilon_{\mathrm{HOMO(AM1)}}$, $-\varepsilon_{\mathrm{HOMO(PM3)}}$, $-\varepsilon_{\mathrm{HOMO(HF)}}$, $-\varepsilon_{\mathrm{HOMO(DFT)}}$ are the values of the negative energies of the highest occupied molecular orbital (HOMO) calculated at AM1, PM3, HF/6-31G* and B3LYP/6-31G* levels, respectively, and $\mathrm{IPv}(E_{\mathrm{cation}} - E_{\mathrm{neutral}})_{\mathrm{DFT}}$ is ionization potentials calculated at B3LYP/6-31G* level (see Table 3). The $-\varepsilon_{\mathrm{HOMO(AM1)}}$, $-\varepsilon_{\mathrm{HOMO(PM3)}}$, $-\varepsilon_{\mathrm{HOMO(HF)}}$, $-\varepsilon_{\mathrm{HOMO(DFT)}}$ and IPv represent the ease of electron donation of phenolic compounds. From Table 3 we can observe that in general electron-donating substituents at the ring decreased the IPv which resulted in better antioxidant activity (E_7), while electron-withdrawing substituents increased the IPv which resulted in decreased antioxidant activity. We can also observe that the compound **36** presents the lowest value for IPv at both DFT and HF levels of theory and consequently, this has the highest antioxidant propriety. On the other hand, the molecule **1** presents the highest value for IPv, consequently, this has the lowest antioxidant activity.

The analysis of the models above reveals that both PM3 and AM1 semiempirical methods do not present a good fit and predictive power. If we compare calculated values (Table 3) with those of $\mathrm{IPv}(E_{\mathrm{cation}} - E_{\mathrm{neutral}})_{\mathrm{DFT}}$, we can see that PM3 and AM1 methods overestimate the ionization potential values. The differences are in 0.98–2.20 eV and 0.97–2.01 eV range for PM3 and AM1 methods, respectively. Comparing HOMO's energies calculated with several quantum models verify that the results of semiempirical methods (AM1 and PM3) are poor to describe the phenol's antioxidant properties for these compounds.

Of the five models presented above, Eq. (10) is the one that presents the best quality statistics, or either, the highest values for significance ($F = 89.69$) and previsibility ($Q^2 = 0.70$) and the lowest value for error of prediction ($S_{\mathrm{PRESS}} = 0.021$). The fit of Eq. (10) is shown in Table 4 and we can see the agreement between the observed and calculated values that are satisfactory. It is interesting to mention that the HOMO's energy has been important in SAR studies of compounds against tumor cells activity [31] and, recently, we have used IPv in our QSAR and SAR studies for compounds with anti-HIV activity [32,33].

We can also observe that the $-\varepsilon_{\mathrm{HOMO(HF)}}$ energy overestimates slightly the $\mathrm{IPv}(E_{\mathrm{cation}} - E_{\mathrm{neutral}})_{\mathrm{DFT}}$ values, while the $-\varepsilon_{\mathrm{HOMO(DFT)}}$ energy underestimates by far these values. It is interesting to note that in most cases the $\mathrm{IPv}(E_{\mathrm{cation}} - E_{\mathrm{neutral}})_{\mathrm{DFT}}$ value is located within the interval defined by the KS (Kohn–Sham) and HF (Hartree–Fock) methodologies, recently, Toro-Labbé and coworkers have suggested that they can be used to identify the range in which the $\mathrm{IPv}(E_{\mathrm{cation}} - E_{\mathrm{neutral}})_{\mathrm{DFT}}$ value is expected to be found [34].

Table 4
Observed, predict and residual values by using Eqs. (10) and (12)

Compound	Observed	Eq. (10)		Eq. (12)	
		Predicted	Residual	Predicted	Residual
1	1.23	1.23	0.00	1.26	−0.03
2	1.15	1.12	0.03	1.13	0.02
3	1.13	1.08	0.05	1.10	0.04
4	1.13	1.18	−0.05	1.17	−0.04
5	1.12	0.98	0.14	1.03	0.09
6	1.11	1.14	−0.03	1.12	−0.02
7	1.04	1.04	0.00	1.08	−0.04
8	0.98	0.99	−0.01	1.01	−0.03
9	0.97	0.85	0.12	0.88	0.09
10	0.96	0.88	0.08	0.93	0.03
11	0.94	0.90	0.04	0.94	0.00
12	0.93	0.84	0.09	0.86	0.07
13	0.89	0.87	0.02	0.90	−0.01
14	0.89	0.94	−0.05	0.98	−0.09
15	0.87	0.76	0.11	0.80	0.07
16	0.85	0.69	0.16	–	–
17	0.85	0.82	0.03	0.84	0.01
18	0.84	0.73	0.11	0.76	0.08
19	0.84	0.78	0.06	0.80	0.04
20	0.84	0.72	0.12	0.80	0.05
21	0.82	0.80	0.02	0.84	−0.02
22	0.81	0.78	0.03	0.81	0.01
23	0.77	0.65	0.12	0.81	−0.04
24	0.73	0.61	0.12	0.66	0.07
25	0.67	0.61	0.06	0.65	0.02
26	0.66	0.66	0.00	0.70	−0.04
27	0.62	0.57	0.05	0.64	−0.02
28	0.60	0.88	−0.28	0.71	−0.11
29	0.58	0.57	0.01	0.66	−0.08
30	0.58	0.65	−0.07	0.47	0.11
31	0.56	0.79	−0.23	0.55	0.01
32	0.54	0.81	−0.27	0.66	−0.12
33	0.53	0.72	−0.19	0.53	0.00
34	0.52	0.67	−0.15	0.49	0.03
35	0.46	0.63	−0.17	–	–
36	0.41	0.47	−0.06	0.54	−0.13

Koopman's theorem (KT), which equates the IP to the negative value of the orbital energy, has traditionally been applied to calculate IPv using the molecular orbital theory. KT is valid only when there is no difference between the orbitals of parent and ionized molecules, since this is never the case in reality, molecular orbital theory provides us with just an approximation, and the results of this approximation are not quantitatively reliable because KT does not take into account electron correlation and orbital relaxation effects [35]. In Table 2 we can observe that $-\varepsilon_{\mathrm{HOMO}}$ calculated at both HF and B3LYP theory levels are correlated with E_7. Therefore, there is a linear dependence between ones, $E_7 = f(\varepsilon_{\mathrm{HOMO}})$, that permit to evaluate E_7 based on HOMO energy, these results are in accordance with Koopman's theorem.

3.2. Multiple linear regression model

A number of models can be obtained using E_7 as dependent variable and calculated properties as independent variables. Therefore, the stepwise multiple regression procedure, based on the forward-selection and backward-elimination methods, was used for variable selection with the purpose to obtain the best regression model (in such a way that variables that swallow little increment are redundant in the explanation of the dependent variable (E_7) which were not included). In order to avoid overfitting or difficulties in interpretation of the resulting models, pairs of variables with $r \geq 0.7$ were classified as intercorrelated ones, and only one of the variables was included in the model.

In a preliminary analysis two properties were important, the $-\varepsilon$ $_{\text{HOMO(DFT)}}$ and the charges on oxygen atom 7. However, the results indicated compounds **16** and **35** to be an outlier for the best model. The standardized residual associated with molecules **16** and **35** were the highest and greater than two; values of standardized residual above two are characteristics of outlier. It is common practice in QSAR studies to omit outliers in the spirit of exploratory data analysis. Hence, the compounds **16** and **35** were excluded from the model with the remaining 34 molecules. After these considerations, the following model was obtained:

$$
\begin{aligned}
E_7 = {} & 3.81(\pm 0.63) + 0.27(\pm 0.02) \\
& -\varepsilon_{\text{HOMO(DFT)}} + 7.09(\pm 0.82)\ \text{O7} \\
& n = 34,\ R^2 = 0.92,\ s = 0.062,\ F = 183.09, \\
& \text{PRESS} = 0.150,\ Q^2 = 0.91,\ S_{\text{PRESS}} = 0.011 \qquad (12)
\end{aligned}
$$

The evaluation of statistical quality of Eq. (12) is very good and accounts for 92% of the variance in E_7, 91% of the predictive capability and high significance. This model shows that O7 has very important role in the variation of E_7. The Eq. (12) shows that, for the set of compounds studied in this work, low values of $\text{IPv}_{\text{HOMO(DFT)}}$ combined with negative charges on atom O7 lead to an increase in the antioxidant activity.

From Table 4 and Fig. 1 we can see that the agreement between the observed and calculated values are satisfactory. In order to verify the prediction power of the model we used Eq. (12) for remaining five phenols compounds (**37**–**41**) to obtain their antioxidant properties. Table 5 shows the prediction values obtained for the test set with Eq. (12). We can observe that this model presented good prediction power. Here, it is interesting to mention that the variables $-\varepsilon_{\text{HOMO(DFT)}}$ and atomic charge of O7 are electronic descriptors, what it reinforces is that electronic effects have a very important role in mechanism by which an antioxidant can deactivate a free radical by electron transfer.

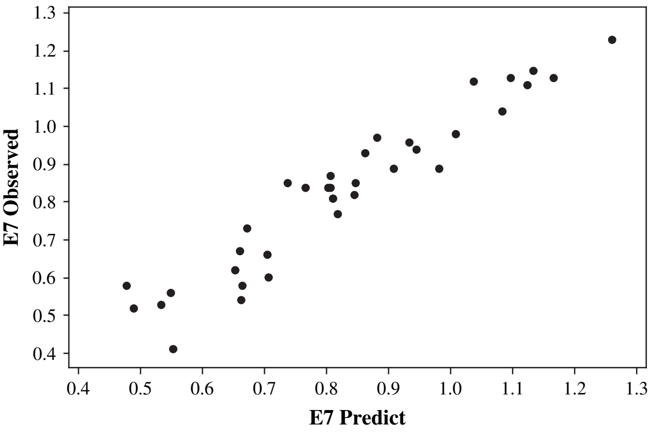


Fig. 1. Observed vs. predict values by using Eq (12).

Table 5
Observed and predicted values for test set by using Eq. (12)

Compound	Observed	Predicted	Residual
37	1.17	1.15	0.02
38	1.06	1.06	0.00
39	0.80	0.80	0.00
40	0.77	0.78	−0.01
41	0.68	0.79	−0.11

4. Conclusions

Descriptors (variables) of physical and electronic properties of potential relevant to the antioxidant activity have been examined for 41 phenolic compounds using quantum mechanical calculations at the AM1, PM3, Hartree–Fock and B3LYP levels of theory. We observed that electron-donating substituents at the ring decreased the IPv resulted in better antioxidant activity, while electron-withdrawing substituents increased the IPv lead to a decreased in ones. The regression equations obtained were based on the following descriptors: energies of the highest occupied molecular orbital ($-\varepsilon_{\text{HOMO}}$) calculated at both HF and DFT/B3LYP levels, respectively, the ionization potentials calculated at DFT/B3LYP level and charge on oxygen atom of the neutral molecule obtained with both HF and DFT/B3LYP levels. The best regression obtained showed not only statistical significance but also predictive ability and revealed that low values of $\text{IPv}_{\text{HOMO(DFT)}}$ combined with negative charges on atom O7 lead to an increase in the antioxidant activity. Here, it is interesting to mention that the variables $\text{IPv}_{\text{HOMO(DFT)}}$ and atomic charge O7 are electronic descriptors, what it reinforces that electronic effects have a very important role mechanism by which an antioxidant can deactivate a free radical by electron transfer.

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References

[1] C.A. Rice-Evans, A.T. Diplock, Free Radic. Biol. Med. 15 (1993) 77.
[2] E. Cadenas, L. Packer, Handbook of Antioxidants, Marcel Dekker, Inc., New York, 1996.
[3] C.A. Rice-Evans, L. Packer, Flavonoids in Health and Disease, Marcel Dekker, Inc., New York, 1998.
[4] S.V. Jovanovic, M. Tosic, M.G. Simic, J. Phys. Chem. 95 (1991) 10824.
[5] H.G. Shertzer, M.W. Tabor, I.T.D. Hogan, S.J. Brown, M. Sainsburg, Arch. Toxicol. 70 (1996) 830.
[6] S.A.B.E. van Acker, M.J. de Groot, D. van den Berg, M.N.J.L. Tromp, G.D. den Kelder, W.J.F. van der Vijgh, A. Bast, Chem. Res. Toxicol. 9 (1996) 1305.
[7] G. Cao, E. Sofic, R.L. Prior, Free Radic. Biol. Med. 22 (1997) 749.

[8] L.F. Wang, H.Y. Zang, Bioorg. Med. Chem. Lett. 14 (2004) 2609.
[9] B. Modak, M.L. Contreras, F. González-Nilo, R. Torres, Bioorg. Med. Chem. Lett. 15 (2005) 309.
[10] E.S. Lien, S. Ren, H.H. Bui, R. Wang, Free Radic. Biol. Med. 26 (1999) 285.
[11] S. Steenken, P. Neta, J. Phys. Chem. 86 (1982) 3661.
[12] S.V. Jovanovic, S. Steenken, M.G. Simic, Y. Hara, Antioxidant properties of flavonoids: Reduction potentials and electron transfer reductions of flavonoid radicals, in: C.A. Rice-Evans, L. Packers (Eds.), Flavonoids in Health and Disease, Marcel Dekker, Inc., New York, 1998.
[13] B.R. Kowalski, Chemometrics: Mathematics and Statistics in Chemistry, D. Reidel Publ Comp., Dordrecht, 1984.
[14] T. Koopman, Physica 1 (1933) 104.
[15] C. Lee, W. Yang, R.G. Parr, Phys. Rev. B37 (1988) 785.
[16] A.D. Becke, J. Chem. Phys. 98 (1993) 5648.
[17] A.D. Becke, J. Chem. Phys. 98 (1993) 1372.
[18] C.C.J. Roothan, Rev. Mod. Phys. 23 (1951) 69.
[19] J.A. Pople, R.K. Nesbet, J. Chem. Phys. 22 (1954) 571.
[20] R. McWeeny, G. Dierksen, J. Chem. Phys. 49 (1968) 4852.
[21] M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, J.J.P. Stewart, J. Am. Chem. Soc. 107 (1985) 3902.
[22] J.J.P. Stewart, J. Comput. Chem. 10 (1989) 209.
[23] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision C.02, Gaussian, Inc., Wallingford, CT, 2004.
[24] CS Chem3D Ultra Molecular Modeling and analyses, Cambridge soft, 2005.
[25] W. Kohn, A.D. Becke, R.G. Parr, J. Phys. Chem. 10 (1996) 12974.
[26] R.G. Parr, R.G. Pearson, J. Am. Chem. Soc. 105 (1983) 7512.
[27] R.G. Parr, L.V. Szentpaly, S. Liu, J. Am. Chem. Soc. 121 (1999) 1922.
[28] P.K. Chattaraj, H. Lee, R.G. Parr, J. Am. Chem. Soc. 113 (1991) 1855.
[29] MINITAB Release 14 for Window, 2003.
[30] F.G. Bordwell, J.P. Cheng, J. Am. Chem. Soc. 113 (1991) 1736.
[31] H.-L. Yang, G.-h. Chen, Y.-q. Li, Eur. J. Med. Chem. 40 (2005) 972.
[32] J. Lameira, C.N. Alves, V. Moliner, E. Silla, Eur. J. Med. Chem. 41 (2006) 616.
[33] J. Lameira, I.G. Medeiros, M. Reis, A.S. Santos, C.N. Alves, Bioorg. Med. Chem. 14 (2006) 7105.
[34] J. Zevallos, A. Toro-Labbé, J. Chil. Chem. Soc. 48 (2003) 39.
[35] D. Danovich, J. Mol. Struct. 401 (1997) 235.