J Mol Model (2019) 25: 200
https://doi.org/10.1007/s00894-019-4083-7

ORIGINAL PAPER

Theoretical study of the antioxidant capacity of the flavonoids present in the *Annona muricata* (Soursop) leaves

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Received: 4 February 2019 / Accepted: 28 May 2019 / Published online: 25 June 2019

Abstract

A theoretical approach was used to evaluate the antioxidant capacity of 20 flavonoids reported in *Annona muricata* leaves. The theoretical study was at the GGA level using the wB97XD functional and the cc-pvtz basis set. The calculations were performed in gas phase and implicit solvent phase. The flavonol robinetin (**03c**) and the flavanol gallocatechin (**01c**) are species that exhibited the best antioxidant capacity in the *HAT*, *SEPT*, and *SPLET* mechanisms. On the other hand, in the *SET* I mechanism, flavonol quercetin (**03b**) was the best, and in the *SET* II mechanism, the most favored species is the flavanol catechin (**01a**). However, these species do not achieve to overcome the antioxidant capacity presented by the Trolox.

Keywords GGA · DFT · Flavonoids · *Annona muricata* · Soursop · HAT · SEPT · SPLET · SET

Introduction

In recent years, several research groups have been studying the relationship that might exist between the life quality of people and the components of the diet they ingest [1]. Likewise, it has been determined that the diet could have a link to the incidence of some diseases. Oxidative stress at the cellular level seems to be related to the emergence of noncontagious diseases such as cancer, diabetes, Alzheimer's and Parkinson's among others, or degenerative processes such as premature aging. These diseases and processes have a high social cost [2] for patients as well as for their relatives.

Oxidative stress is a biological disequilibrium caused by an excess or accumulation of free radicals in the organism [3]. From an electronic point of view, a free radical is a molecule or chemical species that possesses an unpaired electron in its last occupied orbital, which provides it a high instability and therefore an increase in its reactivity [4]. In order to stabilize these molecules, the organisms generate chain oxidation-reduction reactions that involve several biomolecules at cellular level, these structural modifications cause the biomolecules to lose their normal functionality, in such a way that cell damage is caused [5, 6]. Normally, free radicals are produced in the aerobic metabolism of any organism in tolerable amounts by the cell. However, the contamination, rhythm of life, and the intake of toxic products to which the population is continually exposed, increase the oxidative stress and therefore the amount of present free radicals [7].

The study of compounds capable of reducing oxidative stress, called antioxidants, has been increased in recent years [8]. These compounds may have a capacity for prevention, although it has not been proven conclusively. An antioxidant is a molecule capable of inhibiting a free radical (in this case they are called primary antioxidants) or of repairing the damage produced on other molecules (called secondary antioxidants) [2, 3]. In the body, antioxidants can be found endogenously. However, in many cases, its antioxidant capacity is decreased by the effect of some pathology [4]. Moreover, several types of analogous antioxidants are found as bioactive components in numerous plant species, increasing scientific interest, and currently,

This paper belongs to Topical Collection QUITEL 2018 (44th Congress of Theoretical Chemists of Latin Expression)

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they present a high commercial demand in its form of nutraceuticals [1, 6]. It is for this reason that the pharmaceutical industry has focused on the search for more efficient antioxidants which implies that they exhibit high anti-radical activity and high stability after reacting [4, 9, 10]. These products can be found on the market as antioxidant supplements or nutraceutical products that are used both in prevention therapies and in complementary treatments [1, 8, 11].

A plant of tropical origin, commonly called Soursop (*Annona muricata*), in the alternative therapies, has been considered as a plant with medicinal properties [12, 13]. Due to this, the interest to study this plant in a systematic way has increased substantially. Therefore, the nutraceutical products derived from this plant have achieved wide acceptance in the world market of functional foods. However, most of the scientific information reported is still quite general [14–16]. Experimental reports have shown that the leaves of *A. muricata* are an important source of flavonoids [13, 14, 16–20]. Flavonoids are polyphenolic compounds that have a common phenyl benzopyran skeleton (see Fig. 1) and their structural classification depends on the presence of different substituents whose reactivity is subordinated to the present functional groups [1, 8, 21–26]. Normally, the flavonoids found in the leaves are in the form of glycosylated flavonoids or flavonoid glycosides [21, 27–29]. Additionally, it has been shown that they are able to act as antioxidants against reactive oxygen species (*ROS*), through an anti-radical activity, which is conferred by the phenolic OH groups, and the double bonds present in their fundamental chemical structure [22, 30–34]. Recent epidemiological studies [8, 21, 24], propose that a diet high in flavonoids and derivatives might be associated with a low incidence of diseases, as well as an increase in longevity [27, 35, 36].

Galano and coworkers [37] reported that the most important reaction mechanisms involving flavonoids and their derivatives are: (a) hydrogen atom transfer (*HAT*), (b) single electron transfer (*SET*), (c) sequential electron proton transfer (*SEPT*), and (d) sequential proton loss electron transfer (*SPLET*) [38–41].

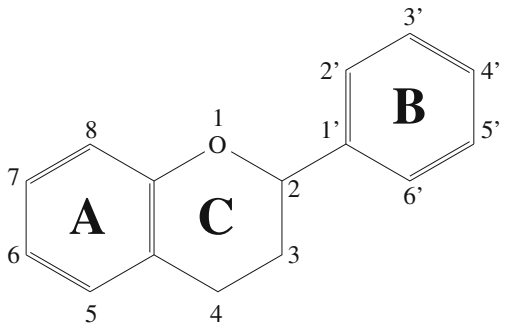

Fig. 1 Common skeleton of the chemical structure of flavonoids

HAT: this mechanism proposes that the flavonoid yields a hydrogen atom, which is captured by the free radical. The rupture is thought to be homolytic of one of the hydroxyl groups (see Eq. 1). As a result, the flavonoid is transformed into a phenoxyl radical. It is expected that this is a less reactive species than the initial radical. Likewise, the free radical is stabilized by the capture of hydrogen generated homolytically.

$$Flav - OH + R^{\bullet} \rightarrow Flav - O^{\bullet} + RH \tag{1}$$

SET: this mechanism proposes that there might be two different pathways, which will depend on the capacity of the antioxidant, which could accept or donate an electron. Moreover, in both routes, the results of the reaction process are two ionized products. In the first path, the flavonoid yields an electron to the free radical (*SET* I), where the flavonoid is transformed into a radical cation, which can exhibit a lower reactivity, and the free radical is transformed into an anionic species (see Eq. 2). In the second route, the free radical yields an electron to the flavonoid (*SET* II), where the flavonoid is transformed into a radical anion that can exhibit a lower reactivity. Likewise, the free radical becomes a cationic species (see Eq. 3).

$$Flav - OH + R^{\bullet} \rightarrow Flav - OH^{\bullet+} + R^{-} \tag{2}$$

$$Flav - OH + R^{\bullet} \rightarrow Flav - OH^{\bullet-} + R^{+} \tag{3}$$

SEPT, this mechanism proposes two consecutive steps or stages. In the first step, the reaction is similar to the *SET* I mechanism, in which the flavonoid yields an electron to the free radical, forming a radical cation and an anion as reaction intermediates (see Eq. 4). In the second stage of the mechanism, the flavonoid radical cation formed in the previous step loses the proton of the hydroxyl group concentrating the electronic density of the radical, and since an anionic and a cationic species are present in the medium, they inevitably decay to a neutral species, resulting in the same reaction products of the *HAT* mechanism (see Eq. 5).

$$Flav - OH + R^{\bullet} \rightarrow Flav - OH^{\bullet+} + R^{-} \tag{4}$$

$$Flav - OH^{\bullet+} \rightarrow Flav - O^{\bullet} + H^{+} \tag{5}$$

SPLET: this mechanism proposes two consecutive stages in its reaction process, but in reverse order to the *SEPT* mechanism. Thus, in the first stage, the flavonoid loses a proton due to the effect of the medium, in the way of a heterolytic rupture, forming a flavonoid anion as a reaction intermediate (see Eq. 6). In the second stage of the proposed mechanism, the flavonoid in its anionic form transfers an electron to the free radical (see Eq. 7), and finally, in the solution the ions of opposite charges are neutralized,

resulting also in the same reaction products of the *HAT* mechanism.

$$Flav - OH \rightarrow Flav - O^- + H^+ \quad (6)$$

$$Flav - O^- + R^\bullet \rightarrow Flav - O^\bullet + R^- \quad (7)$$

On the other hand, although the evaluation of the antioxidant capacity of several compounds has been developed through reliable experimental methods, there are still limitations that the same practice can not avoid [32, 42, 43], such as the variation in the values of the antioxidant capacity, which fluctuate depending on the method. The most important problem, however, is that to determine the antioxidant capacity, we must isolate each one of the components, and that makes investigations very difficult. Many times, this has led to reporting only the values of the antioxidant capacity of mixtures present in the extracts of the plants.

In order to evaluate many of the proposed mechanisms, experimental results are limited. Through the use of computational calculations, the required data can be found with great precision with respect to the experimental data. Therefore, computational chemistry is gaining relevance in antioxidant research, as an innovative strategy shortening steps in experimental studies [44–46]. Computational methods based on calculations of all electrons, such as the density functional theory (*DFT*), make possible the calculation of physicochemical and thermodynamic properties related to the reaction mechanisms of a wide variety of compounds. [47–53]. In this way, computational chemistry is contributing to the analysis and evaluation of the antioxidant capacity of several systems, and thus enables us to understand the relationships that exist between structure and reactivity, which allows us to interpret and complement later in vitro and in vivo studies [41, 54–59]. In the present study, we have evaluated the antioxidant capacity of the flavonoids found in the *Annona muricata* (Soursop) leaves, through the use of quantum mechanical calculations.

Computational details

We studied 20 flavonoids present in the leaves of *A. muricata*, reported by Coria-Téllez and coworkers [13], as well as the Trolox. The molecules were generated in the GaussView 6.0 program [60]. The calculations of quantum mechanics were carried out in Gaussian 16 [61]. The first step consisted of a semi-empirical optimization with AM1 [62]. Subsequently, a DFT approach was made at the GGA level, with the wB97XD functional [63] and the cc-pvtz basis set [64], this is basis set widely recommended in the literature when system have interactions of hydrogen bonds [65], and the vibrational frequencies were analyzed. The second step was to add implicit water (model *SMD*) [66] to the models optimized by *DFT*. It is necessary to introduce the solvent effect for systems in which we wish to study the antioxidant capacity. The third step analyzed intermediate species and products as shown in Eqs. 1 to 7, in gas and solvent phase. The intrinsic reactivity properties [38–41] of bond dissociation enthalpy (*BDE*) (Eq. 8), ionization enthalpy (*IE*) (Eq. 9), enthalpy associated with electronic affinity (*EA*) (Eq. 10), proton dissociation enthalpy (*PDE*) (Eq. 11), enthalpy associated with proton affinity (*PA*) (Eq. 12), and the electron transfer enthalpy (*ETE*) (Eq. 13), were evaluated. A Pearson linear correlation of *BDE*, *IE*, and *ETE* was performed with the experimental value of the percentage of antioxidant activity ($\%A_{antiox}$) of some flavonoids reported by Burda and coworkers [67]. Likewise, the spin density distribution both numerically and graphically was determined for all the radical species of the present study, through a Hirshfeld population analysis.

$$BDE = H_{(Flav-O^\bullet)} + H_{(H^\bullet)} - H_{(Flav-OH)} \quad (8)$$

$$IE = H_{(Flav-OH^{\bullet+})} + H_{(e^-)} - H_{(Flav-OH)} \quad (9)$$

$$EA = H_{(Flav-OH)} - H_{(Flav-OH^{\bullet-})} \quad (10)$$

$$PDE = H_{(Flav-O^\bullet + H_{(H^+)}} - H_{(Flav-OH^{\bullet+})} \quad (11)$$

$$PA = H_{(Flav-O^-)} + H_{(H^+)} - H_{(Flav-OH)} \quad (12)$$

$$ETE = H_{(Flav-O^\bullet)} + H_{(e^-)} - H_{(Flav-O^-)} \quad (13)$$

Results and discussion

We worked with a total of 20 flavonoids; all of them are found in the leaves of the *A. muricata*. The base structure of the flavonoids under study is presented in Fig. 1. For better management, they were identified by means of an ID. In addition, the number and positions of the hydroxyl groups in the structures are shown, as well as the presence of saccharides (see Table 1). Of the 20 structures, three were flavanols, one flavanonol, eight flavonols, five flavones, and three isoflavones (see Fig. 2). Likewise, we worked with the Trolox (see Fig. 3).

From the optimized structures, the bond dissociation enthalpy (*BDE*) was determined for each of the hydroxyl groups present in the 20 species of study. The calculated values of the *BDE* are presented in Table 2, both in gas phase and in solvent phase. In this way, we can identify the hydrogen atoms most susceptible to a homolytic cleavage. The *BDE* values are given in kcal/mol. It can be observed that the solvent effect in some cases favors the process of homolytic cleavage, as well as disadvantage, without being an apparently determining element. In the Table 3, the species by ID with the lowest *BDE* value per flavonoid are shown, which implies that they are the species that can potentially suffer a homolytic cleavage; the *BDE* values are in kcal/mol. We can consider that we can identify by type of

Table 1 Specific structural features of the 20 flavonoids found in the *A. muricata* leaves

Flavonoid	ID	Saccharide	OH[a]	OH					
				3	5	7	3'	4'	5'
Flavanol									
Catechin	01a	–	5	x	x	x	x	x	
Epicatechin	01b	–	5	x	x	x	x	x	
Gallocatechin	01c	–	6	x	x	x	x	x	x
Flavanonol									
Taxifolin	02	–	5	x	x	x	x	x	
Flavonol									
Kaempferol	03a	–	4	x	x	x		x	
Nicotiflorin (Kaempferol 3-O-rutinoside)	03b	di	3		x	x		x	
Robinetin	03c	–	5	x		x	x	x	x
Quercetin	03d	–	5	x	x	x	x	x	
Isoquercetin (Quercetin 3-O-glucoside)	03e	mono	4		x	x	x	x	
Quercetin 3-O-neohesperidoside	03f	di	4		x	x	x	x	
Quercetin 3-O-robinobioside	03g	di	4		x	x	x	x	
Rutin (Quercetin 3-O-rutinoside)	03h	di	4		x	x	x	x	
Flavone									
Homoorientin (Luteolin 6-C-glucoside)	04a	mono	4		x	x	x	x	
Luteolin 7,3'-di-O-glucoside	04b	2 mono	2		x			x	
Vitexin (Apigenin 8-C-glucoside)	04c	mono	3		x	x		x	
Isovitexin (Apigenin 6-C-glucoside)	04d	mono	3		x	x		x	
Tangeretin	04e	–	0						
Isoflavone									
Daidzein	05a	–	2			x		x	
Genistein	05b	–	3		x	x		x	
Glycitein	05c	–	2			x		x	

[a]number of hydroxyl groups

flavonoid, which is the structure that favors the homolytic cleavage, in the case of flavanols is the structure **01b** is favored in the gas phase, but in the solvent phase, the species **01c** is preferred. Likewise, in flavonols, it is the structure **03d** in the gas phase and **03c** in the solvent phase, those favored by its *BDE* value; in the flavones the structure **04a** it is preferred both in gas phase and solvent; in the isoflavones the **05c** in the gas phase and the **05b** in the solvent phase is the favored structures. It should be noted that the Trolox in solvent phase has the lowest value of *BDE*.

In the Table 4, we show the lengths of the intramolecular hydrogen bond that are generated when the radical has been formed, both in gas phase and solvent. This interaction is formed between the oxygen belonging to the hydroxyl most susceptible to the homolytic cleavage (reactive site) and the hydrogen belonging to a nearby hydroxyl. Additionally, the bond length reduction values were found upon a homolytic cleavage of the flavonoids occurs. The bond reduction values in solvent phase were associated with their corresponding *BDE* values, finding an important inverse relation, with an *r* value equal to - 0.8565 (see Fig. 4). This implies that at a lower *BDE* value, the atoms will get closer. Therefore, flavonoids having a higher susceptibility to react by a homolytic cleavage tend to be prone to stabilize by an interaction with the neighboring hydrogen atoms with acid character. The *BDE* value and the approximation of a hydrogen atom with an acid character are indispensable to discuss the *HAT* type mechanism of reaction.

In order to properly understand the *SET* mechanism, it is important to determine the ionization enthalpy (*IE*) values and the enthalpy associated to the electronic affinity (*EA*). These values are linked to the global structures, and we cannot discriminate by centers. These enthalpy values must be interpreted as in thermodynamics; We should interpret that the negative values of the EA, it is associated with releases energy in the process of capturing an electron; if positive, it is related to the energy required to obtain an electron. In the Table 5, the values for both

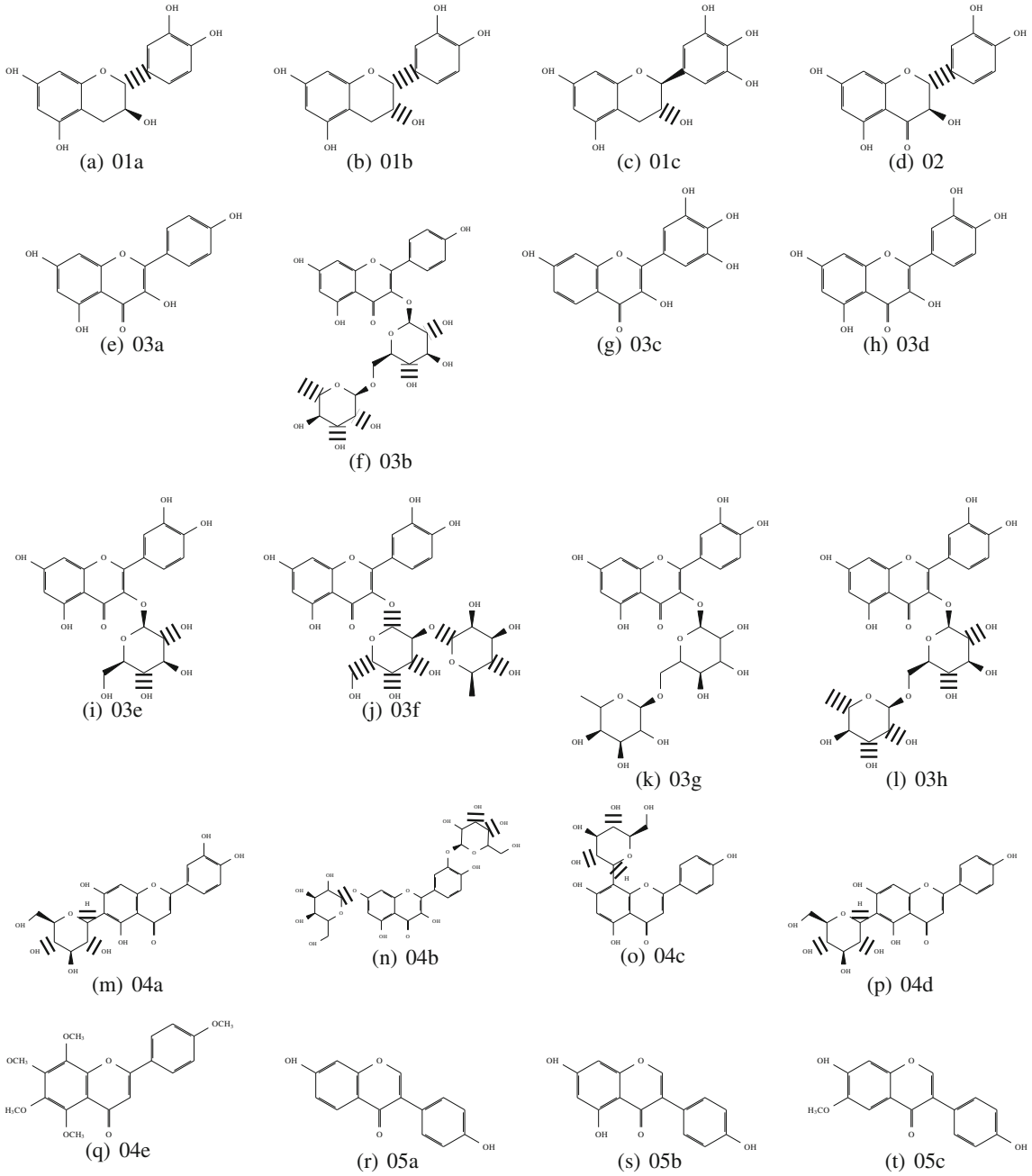

Fig. 2 Chemical structures of flavanols, flavanonols, flavonols, flavonol glycosides, flavones, flavone glycosides, and isoflavones found in *A. muricata* leaves

enthalpies are presented, both in the gas phase and in the solvent phase. It should be noted that for the *IE*, all values in solvent phase tend to favor donor capacity, while for *EA*, the solvent phase makes them more resistant to receive an electron within the system. Regarding the *IE*, the values for the flavanols (01a–01c), in the solvent phase are really very similar, although in the gas phase there is a range of 3 kcal/mol, while for the flavonols (03a–03h), in the solvent phase they are in a range of 6 kcal/mol, and in gas phase with a range of 14 kcal/mol, flavones (04a–04e), in gas phase present values in a range of 11 kcal/mol and in solvent phase in a range of 12 kcal/mol. Finally, for isoflavones (05a–05c), the values oscillate between 4 kcal/mol in the solvent phase and 2 kcal/mol in gas phase. It is important to note that the *IE* value of the Trolox is the lowest in both gas phase and solvent phase. When we analyze the EA, the flavanols (01a–01c), in the solvent phase present values in a range of 30 kcal/mol, and

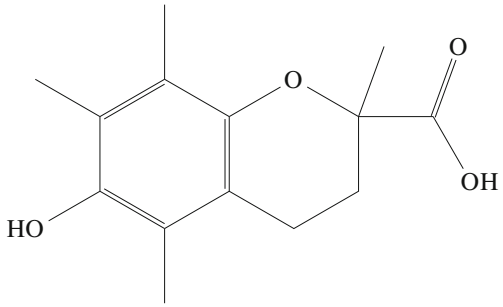

Fig. 3 Chemical structure of Trolox (06)

the gas phase it is negative in the rank of 14 kcal/mol. In the event of the flavonols (03a–03h) in the solvent phase, present values in a range of 3 kcal/mol and the gas phase have a rank of 31 kcal/mol. For flavones (04a–04e), the values in the solvent phase have a range of 6 kcal/mol and the gas phase of 20 kcal/mol. Lastly, isoflavones (05a–05c) solvent phase, have a rank of 3 kcal/mol and in the gas phase of 5 kcal/mol. In the case of the Trolox, the value is negative in the gas phase and positive in the solvent phase, but in both cases, they are the lowest values in the data set.

In the *SEPT* mechanism, the *IE* values, and the proton dissociation enthalpy (*PDE*) values were determined, which are presented in the Table 6. In all cases, the values in the solvent phase are much higher than in the gas phase for the *PDE*, which implies that in the solvent phase, the radical cation species are much more stable, likely due that to the polar medium. In the case of the species **04e**, there are no *PDE* values since it does not have hydroxyl groups.

Table 2 *BDE* of the several OH groups found in the flavonoids and Trolox

ID	BDE[a]		ID	BDE[a]		ID	BDE[a]	
	Gas	Solvent		Gas	Solvent		Gas	Solvent
01a			01b			01c		
3-OH	106.66	110.52	3-OH	103.88	106.36	3-OH	101.45	118.59
5-OH	84.39	85.40	5-OH	84.07	109.43	5-OH	82.47	108.51
7-OH	84.91	85.38	7-OH	84.15	85.24	7-OH	84.02	110.04
3'-OH	84.38	82.59	3'-OH	85.00	82.26	3'-OH	76.64	81.21
4'-OH	74.97	79.57	4'-OH	75.50	79.27	4'-OH	75.61	76.89
						5'-OH	84.66	82.62
02			03a			03b		
3-OH	106.75	112.30	3-OH	75.11	77.95	5-OH	101.01	86.02
5-OH	99.20	93.83	5-OH	101.02	93.40	7-OH	88.11	90.44
7-OH	96.06	104.01	7-OH	106.44	92.19	4'-OH	85.69	88.17
3'-OH	84.67	83.02	4'-OH	85.57	87.82			
4'-OH	75.82	80.32						
03c			03d			03e		
3-OH	83.20	81.30	3-OH	83.99	80.45	5-OH	85.97	92.68
7-OH	88.55	91.63	5-OH	86.00	87.26	7-OH	88.25	92.68
3'-OH	85.78	84.15	7-OH	88.37	91.78	3'-OH	84.34	83.47
4'-OH	75.43	76.89	3'-OH	84.86	83.64	4'-OH	74.66	80.27
5'-OH	78.61	82.00	4'-OH	73.66	79.12			
03f			03g			03h		
5-OH	101.69	94.91	5-OH	96.94	88.87	5-OH	91.08	96.57
7-OH	91.00	93.31	7-OH	95.58	93.17	7-OH	88.70	100.18
3'-OH	85.75	83.98	3'-OH	93.08	84.22	3'-OH	84.47	92.57
4'-OH	76.60	81.09	4'-OH	75.13	80.53	4'-OH	78.14	80.57
04a			04b			04c		
5-OH	82.14	85.14	5-OH	85.58	88.31	5-OH	87.38	89.08
7-OH	92.12	96.44	4'-OH	81.82	83.74	7-OH	87.03	92.31
3'-OH	85.34	84.05				4'-OH	85.04	87.01
4'-OH	74.98	80.67						
04d			05a			05b		
5-OH	82.20	84.94	7-OH	88.55	92.26	5-OH	88.94	88.75
7-OH	91.19	96.06	4'-OH	84.09	85.72	7-OH	89.44	93.03
4'-OH	84.29	87.60				4'-OH	83.84	85.54
05c			06					
7-OH	87.66	87.31	1-OH	106.14	84.25			
4'-OH	83.93	85.63	6-OH	75.24	75.84			

[a]In kcal/mol

Table 3 *BDE* of the reactive sites of the flavonoids and Trolox

ID	OH[a]	BDE[b]		ID	OH[a]	BDE[b]	
		Gas	Solvent			Gas	Solvent
01a	4'	74.97	79.57	03h	4'	78.14	80.57
01b	4'	75.50	79.27	04a	4'	74.98	80.67
01c	4'	75.61	76.89	04b	4'	81.82	83.74
02	4'	75.82	80.32	04c	4'	85.04	87.01
03a	3	75.11	77.95	04d	5	82.20	84.94
03b	4'	85.69	88.17	04e	–	–	–
03c	4'	75.43	76.89	05a	4'	84.09	85.72
03d	4'	73.66	79.12	05b	4'	83.84	85.54
03e	4'	74.66	80.27	05c	4'	83.93	85.63
03f	4'	76.60	81.09	06	6	75.24	75.84
03g	4'	75.13	80.53				

[a]Position of the hydroxyl groups
[b]In kcal/mol

Furthermore, it was determined the enthalpy associated with the proton affinity (*PA*) values and the electron transfer enthalpy (*ETE*) values, which are linked to the *SPLET* mechanism. These values are shown in Table 7, both for gas phase and for solvent phase. In most cases, the *PA* values are increased when the flavonoids are in the solvent phase. Oppositely, in the isoflavones and the Trolox, the decreases in the PA values tend apparently to favor a heterolytic rupture of the proton. On the other hand, the *ETE* values increase in all cases when the species are in the solvent phase. In addition, in flavanols, the species **1c** is the one presenting a greater susceptibility to donate an electron from its anionic form, both in the gas phase and in the solvent phase. Likewise, in the flavonols, the species **03c** is favored in both phases, together with **03a** in solvent phase only. In the case of flavones, the structure **04a** is the favored species in the gas phase, and the structure **04b** is in the solvent phase. In isoflavones, the favored structure in both phases is the species **05b**. It should be noted that the Trolox has the lowest *ETE* values in gas phase and solvent phase, in

Table 4 Intramolecular hydrogen bond lengths and bond reduction between the reactive site of the flavonoids and a neighbor OH group

ID	OH[a]	Length[b] OH−−OH		Length[b] OH−−O•		Bond reduction[b]		BDE[c] solv. phase
		Gas	Solv.	Gas	Solv.	Gas	Solv.	
01a	4'	2.13	2.19	2.03	2.12	0.10	0.07	79.57
01b	4'	2.14	2.18	2.03	2.13	0.11	0.05	79.27
01c	4'	2.17	2.22	2.03	2.14	0.14	0.08	76.89
02	4'	2.13	2.18	2.03	2.13	0.10	0.05	80.32
03c	4'	2.18	2.22	2.04	2.15	0.14	0.07	76.89
03d	4'	2.14	2.18	2.03	2.13	0.11	0.06	79.12
03e	4'	2.14	2.19	2.03	2.14	0.11	0.05	80.27
03f	4'	2.14	2.18	2.03	2.13	0.11	0.05	81.09
03g	4'	2.14	2.19	2.03	2.14	0.11	0.05	80.53
03h	4'	2.14	2.18	2.03	2.13	0.11	0.05	80.57
04a	4'	2.14	2.19	2.04	2.14	0.10	0.06	80.67

[a]Position of the hydroxyl group
[b]In Å
[c]In kcal/mol

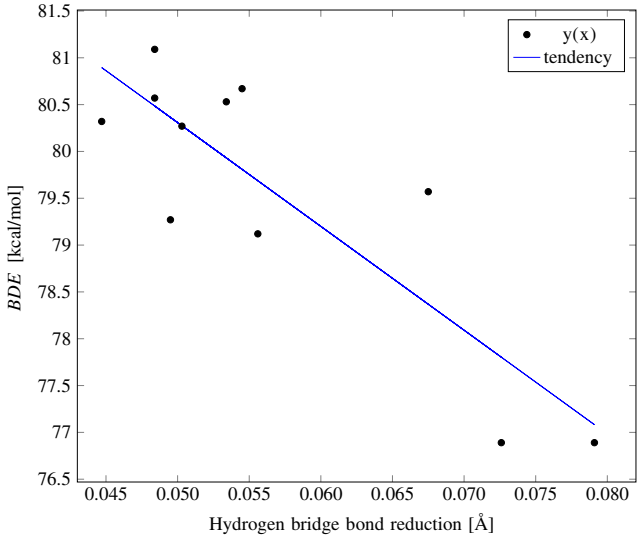

Fig. 4 Correlation between the hydrogen bond reduction in the reactive site and the calculated *BDE*s

comparison with those obtained by the analyzed flavonoids when they are in the anionic form, being opposite to what happened with its *PA* values.

Table 5 *IE* y *EA* of the flavonoids and Trolox

ID	IE[a]		EA[a]	
	Gas	Solvent	Gas	Solvent
01a	238.72	128.38	−14.32	23.42
01b	235.77	128.36	−17.13	25.21
01c	237.10	127.98	−28.75	55.29
02	244.69	129.80	11.64	55.55
03a	240.46	131.00	16.21	56.91
03b	237.69	136.63	29.93	58.49
03c	232.50	126.24	15.43	57.93
03d	229.48	125.37	10.14	55.43
03e	226.46	129.75	9.78	56.71
03f	240.17	131.39	32.53	58.28
03g	227.14	130.80	38.08	57.59
03h	228.12	131.07	7.02	55.83
04a	236.44	131.22	33.65	54.51
04b	230.16	134.61	12.41	50.17
04c	239.67	139.58	12.76	54.56
04d	237.65	137.79	33.35	54.13
04e	241.47	127.71	13.50	56.67
05a	239.71	131.42	5.43	51.94
05b	237.41	130.89	0.63	48.90
05c	237.93	134.14	3.75	50.84
06	225.36	117.39	−27.55	16.28

[a]In kcal/mol

Table 6 *IE* and *PDE* of the reactive sites of the flavonoids and Trolox

ID	OH[a]	IE[b]		PDE[b]	
		Gas	Solvent	Gas	Solvent
01a	4’	238.72	128.38	48.99	143.27
01b	4’	235.77	128.36	52.46	142.99
01c	4’	237.10	127.98	51.24	140.98
02	4’	244.69	129.80	43.87	142.59
03a	3	240.46	131.00	47.38	139.03
03b	4’	237.69	136.63	60.74	143.63
03c	4’	232.50	126.24	55.67	142.73
03d	4’	229.48	125.37	56.92	145.83
03e	4’	226.46	129.75	60.94	142.60
03f	4’	240.17	131.39	49.16	141.77
03g	4’	227.14	130.80	60.72	141.81
03h	4’	228.12	131.07	62.76	141.58
04a	4’	236.44	131.22	51.28	141.53
04b	4’	230.16	134.61	64.40	141.20
04c	4’	239.67	139.58	58.10	139.51
04d	5	237.65	137.79	57.29	139.23
04e	–	241.47	127.71	–	–
05a	4’	239.71	131.42	57.12	146.38
05b	4’	237.41	130.89	59.17	146.74
05c	4’	237.93	134.14	58.73	143.57
06	6	225.36	117.39	62.62	150.53

[a]Position of the hydroxyl groups

[b]In kcal/mol

In the Table 8, the experimental percentages of antioxidant activity ($\%A_{antiox}$) values are presented, which were reported for some of the flavonoids of the present job [67].

Table 7 *PA* and *ETE* of the reactive sites of the flavonoids and Trolox

ID	OH[a]	PA[b]		ETE[b]	
		Gas	Solvent	Gas	Solvent
01a	4’	162.56	170.98	125.15	100.67
01b	4’	166.02	171.06	122.22	100.29
01c	4’	169.42	172.01	118.93	96.95
02	4’	165.50	170.36	123.05	102.04
03a	3	164.78	170.22	123.06	99.81
03b	4’	152.96	171.25	145.47	109.00
03c	4’	165.32	169.13	122.86	99.83
03d	4’	162.23	168.47	124.17	102.72
03e	4’	162.98	166.37	124.42	105.98
03f	4’	153.19	167.89	136.15	105.28
03g	4’	158.83	167.64	129.03	104.97
03h	4’	162.50	167.69	128.38	104.96
04a	4’	161.79	167.99	125.93	104.76
04b	4’	163.13	172.09	131.43	103.73
04c	4’	157.45	170.29	140.32	108.80
04d	5	166.81	165.81	128.13	111.20
04e	–	–	–	–	–
05a	4’	177.93	174.67	118.90	103.13
05b	4’	179.28	174.67	117.30	102.95
05c	4’	178.47	174.73	118.20	102.98
06	6	181.87	178.52	106.11	89.40

[a]Position of the hydroxyl groups

[b]In kcal/mol

Table 8 Experimental $\%A_{antiox}$ reported in some of the analyzed flavonoids and Trolox by Burda and coworkers [67], likewise their corresponding calculated values of *BDE*, *ETE*, *IE* in solvent phase

ID	$\%A_{antiox}$	BDE[a]	IE[a]	ETE[a]
03a	65.3	77.95	131.00	99.81
03c	61.7	76.89	126.24	99.83
03d	63.6	79.12	125.37	102.72
05a	32.9	85.72	131.42	103.13
06	95.8	75.84	117.39	89.40

[a]In kcal/mol

Additionally, we present the values of *BDE*, *IE*, and *ETE* calculated in solvent phase. The three properties reported in this article show an important inverse correlation with $\%A_{antiox}$. It was found that the *BDE* values have the highest inverse relationship with the $\%A_{antiox}$ of the analyzed species, with a value of r equal to - 0.8816 (see Fig. 5), the correlation for the *ETE* values, present an r value of -0.8775 (see Fig. 6). Finally, the *IE* values have a value of r equal to -0.8629 (see Fig. 7). Thereby, it can to be considered that the *BDE* values are those best reflecting the antioxidant capacity of the studied flavonoids concerning the experimental results.

The four mechanisms of antioxidant activity we will analyze only in solvent phase, because it best represents the experiment. Although in our results we did not include the free radical with which the antioxidant should react, the calculations were made for the hydroxyl radical and the superoxide anion radical verifying the feasibility of the reaction, but we do not include them in the present article. In the case of the *HAT* mechanism, taking into account the values of *BDE* and the length of the hydrogen bonds, the flavonoid that presents better characteristics as an antioxidant is the species **03c**, followed by to species **01c**, while difference of the *BDE* values respect to the Trolox is approximately 1.05 kcal/mol in absolute value, in both cases.

In the *SET* mechanism, according to the *IE* determined values, the flavonoid that has better capacity as an antioxidant through the *SET* I path is the species **03d**, and according to the *EA* values, for the *SET* II path is the species

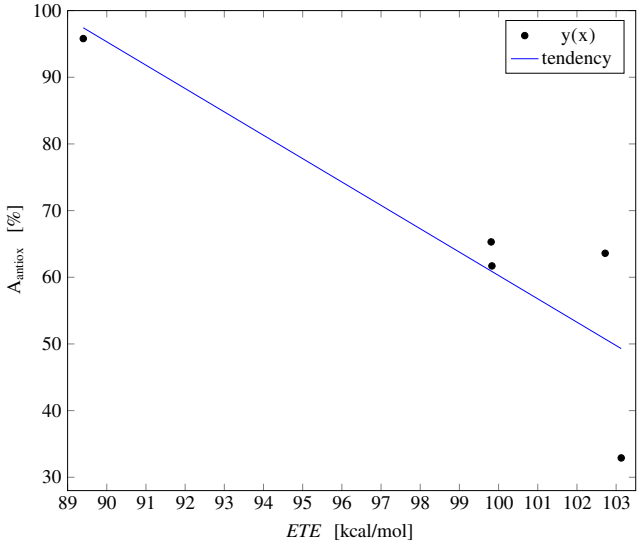

Fig. 6 Correlation between the calculated *ETE*s and the experimental $\%A_{antiox}$ reported in some flavonoids and Trolox by S. Burda and coworkers [67]

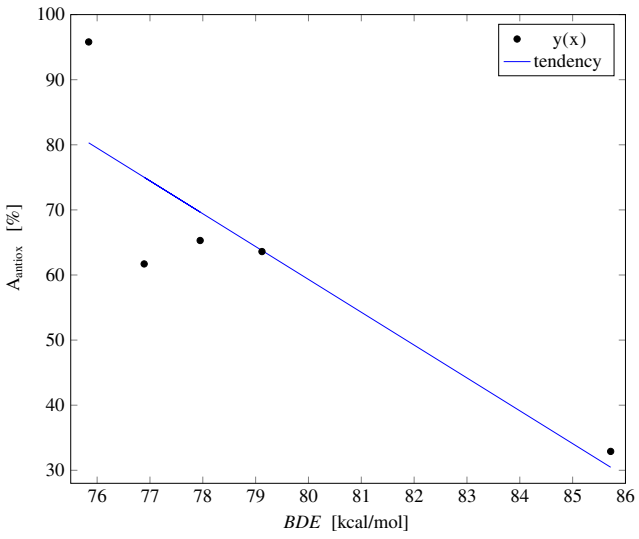

Fig. 5 Correlation between the calculated *BDE*s and the experimental $\%A_{antiox}$ reported in some flavonoids and Trolox by S. Burda and coworkers [67]

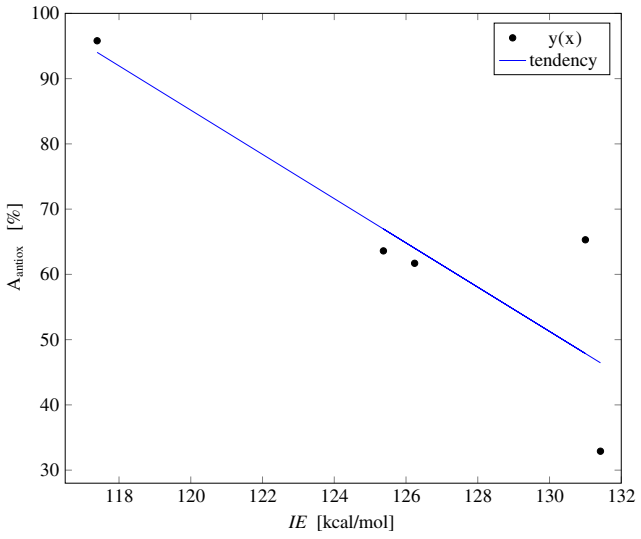

Fig. 7 Correlation between the calculated *IE*s and the experimental $\%A_{antiox}$ reported in some flavonoids and Trolox by S. Burda and coworkers [67]

Table 9 Spin density (ρ_s) of the most reactive atom in the radical form of the flavonoids that shows the best antioxidant capacity and in the radical form of Trolox

ID	Phenoxyl Radical			Cationic Radical			
	ρ_s			ρ_s			
	Atom	Gas	Solv.	Atom	Gas	Atom	Solv.
01a	4'-O	0.30	0.28	C4'	0.22	C4'	0.22
01c	4'-O	0.32	0.30	C4'	0.31	C4'	0.29
03c	4'-O	0.28	0.27	C3	0.24	C4'	0.23
03d	4'-O	0.26	0.25	C3	0.25	C3	0.25
06	6-O	0.31	0.33	C6	0.22	C6	0.22

01a, although in both cases this capacity is lower than that of the Trolox.

Moreover, in the *SEPT* mechanism, the flavonoid that exhibits better antioxidant characteristics by the additivity of the enthalpies (*IE* and *PDE*) is the species **03c**, and very close in value is found the **01c**, in the global, it is the Trolox that exhibits a better enthalpic behavior for this mechanism.

In the *SPLET* mechanism (see Eqs. 6 and 7), according to the determined by the values of both mechanism stages, the flavonoid that has a higher potential as an antioxidant is the species **03c**, and very close it is found the **01c**.

Of the different mechanisms, we can rationalize that the favored species belong to the group of flavonols and flavanols, and they do not present saccharides in their structure. It should be noted that all the flavonoids mentioned exhibit lower antioxidant capacity than that presented by the Trolox. However, the activity of these species is still relevant in each mechanism. We could suppose a consortium activity of the different present species, so that, then, they could show a synergic effect within the organism.

Additionally, the analysis of correlations between the calculated properties and the experimental $\%A_{antiox}$ shows us that *HAT* is the predominant mechanism in the solvent phase, followed by the *SPLET* mechanism, and in last instead, the *SET* mechanism, these results agree with the reaction feasibility, this same reflect the *BDE* values, in comparison with the *IE* and the *ETE* values, so *HAT* was favored energetically over the rest of the mechanisms.

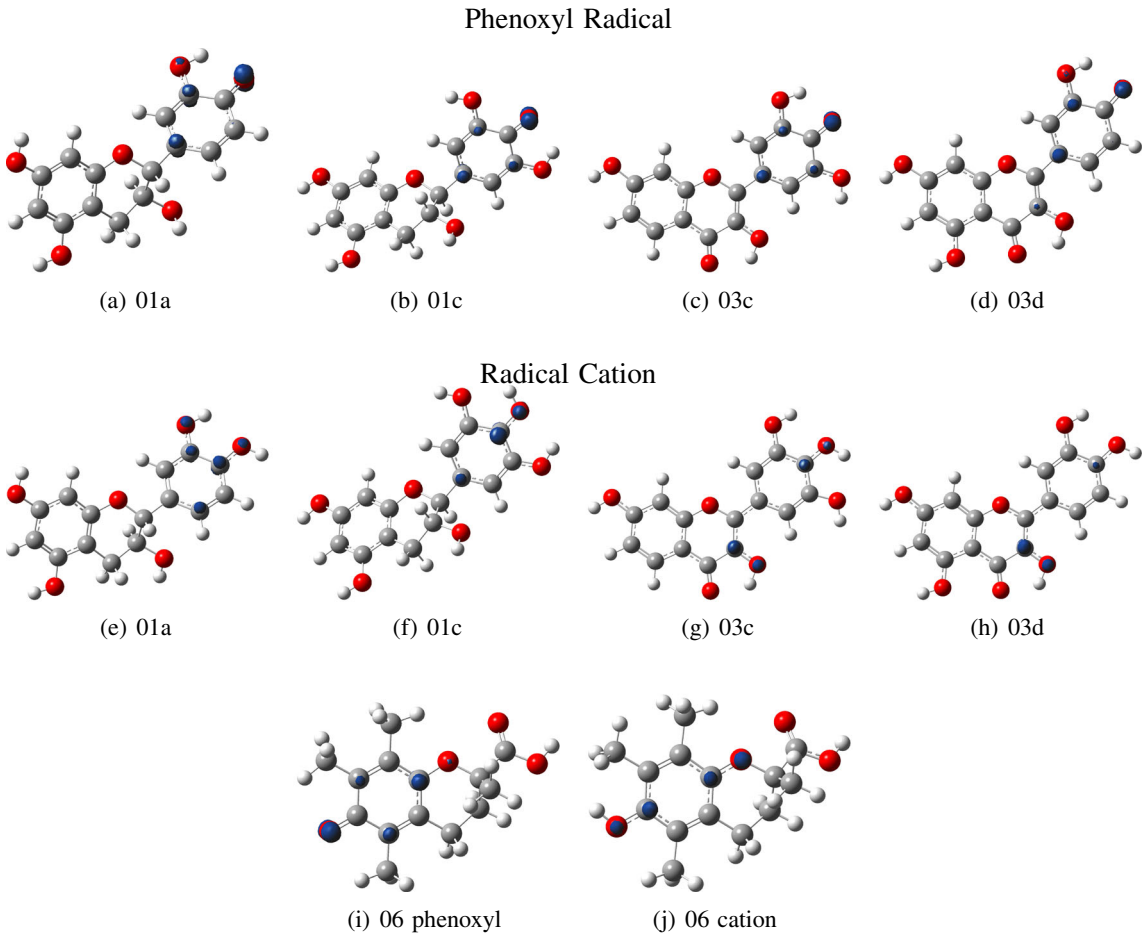

Fig. 8 Highest spin density regions of flavonoids and Trolox (i and j), in the gas phase

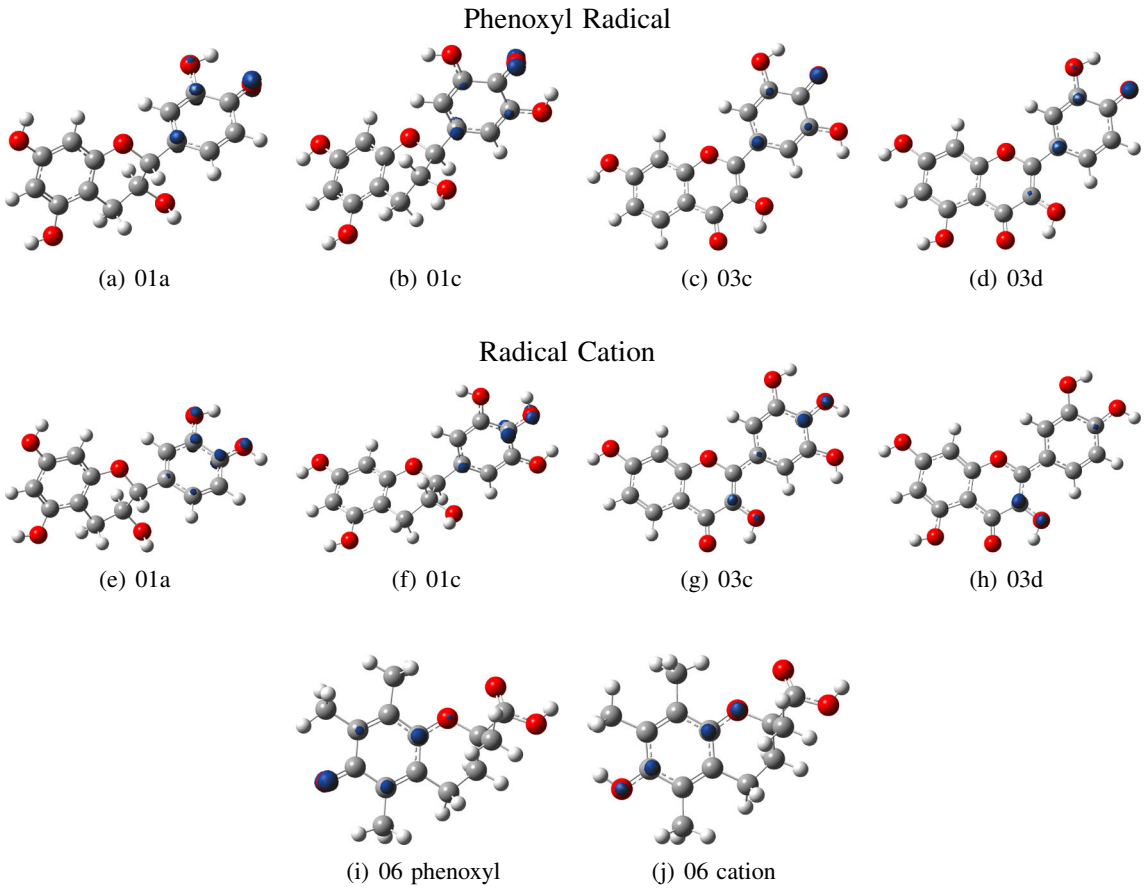

Fig. 9 Highest spin density regions of flavonoids and Trolox (i and j), in the solvent phase

When a compound receives an electron or loses an electron, forming a cationic species, it will exhibit a better antioxidant property when the species itself is able to redistribute the remaining electron density, by the effect of adding an electron or losing an electron. Table 9 shows the numerical values for the spin density of the phenoxyl radical and the radical cation of the species with the highest antioxidant potential. The values we present are only for the atoms that exhibit a maximum value. The radical cation species better distribute the remaining spin density. In the case of phenoxyl radicals, they are also able to redistribute the remainder electronic density, but this capacity is always better in the radical cation form, as we can see from the graphics (Figs. 8 and 9). Depending on the nature of the species, we observed that the values could remain constant, increase or decrease in the solvent phase, not being able to find any particular trend.

Conclusions

The antioxidant capacity of the 20 flavonoids reported in the *Annona muricata* leaves was evaluated from a theoretical approach. It was found that in the solvent phase, flavonol robinetin (**03c**) and flavanol gallocatechin (**01a**) are the species that exhibited the best antioxidant capacity in the *HAT*, *SEPT*, and *SPLET* mechanisms. On the other hand, in the *SET* I mechanism, the best antioxidant species was the flavonol quercetin (**03b**), and in the *SET* II mechanism, the most favored species was the flavanol catechin (**01a**). However, these species fail to overcome the Trolox antioxidant capacity. Furthermore, an important correlation was found between the flavonoids that have a greater susceptibility to a homolytic cleavage (lower *BDE* values) and the interaction with another hydroxyl group (higher approximation between the atoms forming an intramolecular hydrogen bond). In addition, when the *BDE*, *IE*, and *ETE* values were related in solvent phase with some experimental antioxidant activity reported values, the best correlation was obtained with the *BDE* values, showing that *HAT* is the predominant mechanism, which also coincides with its energetic feasibility, compared to the rest of the mechanisms. Finally, according to the spin density distribution analysis, the radical cations showed a higher electronic delocalization capacity than the phenoxyl radicals. This property contributes to the stabilization of these species and is also a desired feature in the evaluation of antioxidant compounds.

Acknowledgments The authors acknowledge the Vice-Rectorate for Research of the Universidad Católica de Santa María for the financial support through the internal project 24975-R-2017.

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