Food Antioxidants: Chemical Insights at the Molecular Level

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Annu. Rev. Food Sci. Technol. 2016. 7:335–52

First published online as a Review in Advance on January 11, 2016

The *Annual Review of Food Science and Technology* is online at food.annualreviews.org

This article's doi: 10.1146/annurev-food-041715-033206

Keywords

antioxidant properties, radical reactions, reaction mechanisms, scavenging ability, density functional theory

Abstract

In this review, we briefly summarize the reliability of the density functional theory (DFT)-based methods to accurately predict the main antioxidant properties and the reaction mechanisms involved in the free radical–scavenging reactions of chemical compounds present in food. The analyzed properties are the bond dissociation energies, in particular those involving OH bonds, electron transfer enthalpies, adiabatic ionization potentials, and proton affinities. The reaction mechanisms are hydrogen-atom transfer, proton-coupled electron transfer, radical adduct formation, single electron transfer, sequential electron proton transfer, proton-loss electron transfer, and proton-loss hydrogen-atom transfer. Furthermore, the chelating ability of these compounds and its role in decreasing or inhibiting the oxidative stress induced by Fe(III) and Cu(II) are considered. Comparisons between theoretical and experimental data confirm that modern theoretical tools are not only able to explain controversial experimental facts but also to predict chemical behavior.

INTRODUCTION

Quantum mechanics–based studies have become an important part of current chemical investigations because they can provide valuable physicochemical insights that help in the understanding of chemical processes at the molecular level. Their accuracy and reliability have been significantly increased in the past few decades because of the rapid improvement of both hardware and software. Today, it is possible to gather a wide variety of data for rather large systems at feasible computational costs. The investigations of the chemical reactions involved in antioxidant activities are no exception. There are numerous studies within this area of research that have been completely or partially conducted using theoretical approaches.

Antioxidants have been reported to exert numerous beneficial effects on human health, including anticancer (Roleira et al. 2015), anti-inflammatory (Parhiz et al. 2015), antibacterial (Widsten et al. 2014), antiviral (Panchal et al. 2012), cardioprotective (Tinkel et al. 2012), and neuroprotective (Danta & Piplani 2014) properties. There is also evidence supporting the potential therapeutic use of antioxidants on diabetes (Marrazzo et al. 2014), osteoporosis (Yan et al. 2014), arthritis (Vysakh et al. 2014), and cataracts (Sunkireddy et al. 2013). Many such beneficial effects have been associated with the ability of antioxidants to inhibit oxidative stress (OS) and the associated molecular damage.

OS is caused by an imbalance between the production and consumption of oxidative species (Sayre et al. 2008), and often involves reactions between free radicals and molecules of high biological importance, such as lipids, proteins, and DNA. Therefore, the study of compounds with free radical–scavenging activity is currently an important area of research. Moreover, the study of the relative scavenging ability of these compounds is of vital importance in understanding their protective effects and also in designing efficient strategies against OS.

Antioxidants are capable of inhibiting the deleterious effects of OS in different ways through a wide variety of mechanisms. Inhibition can be exerted in both enzymatic and nonenzymatic (chemical) ways. Different strategies to establish trends in reactivity are analyzed, and some examples are presented to illustrate how computational approaches can be used to predict structure-activity relationships, as well as to identify the most likely chemical reactions involved in the antioxidant activity and the most efficient protectors against OS.

CHEMICAL CLASSIFICATION OF ANTIOXIDANTS

There is a large variety of natural antioxidants present in food. Among them, those often called phenolics include more than 8,000 compounds, and they all share the structural feature of presenting a phenol moiety. A classification of such compounds depends on the number of phenol subunits: Simple phenols contain only one phenol functionality (e.g., phenolic acids), whereas polyphenols contain two (e.g., flavonoids and stilbenes) or more phenol subunits (e.g., tannins). The basic chemical structure of the most common natural phenolic antioxidants is presented in **Figure 1**.

Phenolic acids hold one carboxylic acid function and two different carbon frameworks, giving rise to the hydroxycinnamic (e.g., p-coumaric, caffeic, ferulic, and sinapic acids) and hydroxybenzoic structures.

Flavonoids are polyphenol substances whose basic structural feature is the flavone (2-phenylbenzo-γ-pyran) nucleus, constituted by two benzene rings (A and B) linked by an oxygen-containing pyran ring (C). Depending on the degree of C-ring oxidation, the hydroxylation pattern of the nucleus, and the substituent at carbon 3 (see **Table 1**), the flavonoids can be further divided into subclasses: isoflavones, flavanols, flavonols, flavanones, anthocyanins, and proanthocyanidins.

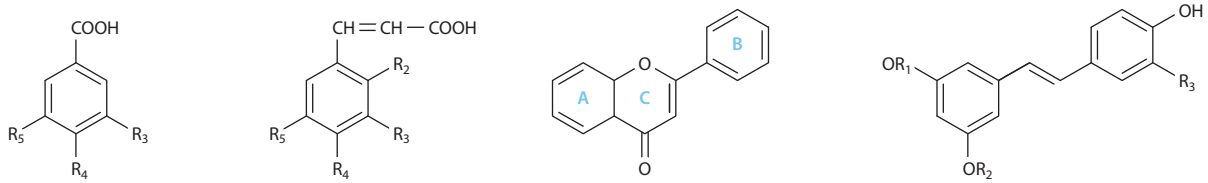


Figure 1

Structures of benzoic and hydroxycinnamic acids, flavonoids, and stilbenes.

A particular subclass of flavonoids, in which the C ring is open, is known as the chalcones. In nature, many flavonoids are glycosylated, and carbohydrate substitutions include D-glucose, L-rhamnose, glucorhamnose, galactose, and arabinose.

Stilbenes (e.g., resveratrol, pterostilbene, and piceatannol) are characterized by a double bond connecting the phenolic rings. As chemical protectors, antioxidants are further classified on the basis of their mode of action as primary (Type I, or chain breaking) or secondary (Type II, or preventive) antioxidants (Chaiyasit et al. 2007). The primary ones are chemical species able to prevent oxidation by acting as free-radical scavengers. In this case, antioxidants directly react with free radicals, producing significantly less reactive species or turning off the radical chain reaction. The type II antioxidants retard the oxidation process by indirect pathways, including metal chelation, decomposition of hydroperoxides to nonradical species, repairing of primary antioxidants by hydrogen or electron donation, deactivation of singlet oxygen or sequestration of triplet oxygen, and absorption of UV radiation. There are also some antioxidants that can be classified as multiple-function antioxidants because their protective effects are exerted by both primary and secondary ways of action.

THE PROPOSED REACTION MECHANISMS

The reaction mechanisms by which the primary and the secondary antioxidants can exert their activity depend on their intrinsic abilities. The possible action mechanisms of the Type I antioxidants are hydrogen-atom transfer (HAT), proton-coupled electron transfer (PCET), radical adduct formation (RAF), single electron transfer (SET), sequential proton-loss electron transfer (SPLET), sequential electron proton transfer (SEPT), and sequential proton-loss hydrogen-atom transfer (SPLHAT).

Table 1 Subclasses of naturally occurring flavonoids and an example of each class

Class	Compound	Substituents					
		3	5	7	3′	4′	5′
Flavonols	Quercetin	OH	OH	OH	OH	OH	H
Flavononoles	Taxifolin	OH	OH	OH	OH	OH	H
Flavones	Luteolin	H	OH	OH	OH	OH	H
Flavonoles	Catechin	OH	OH	OH	OH	OH	H
Chalcones	Phloretin	OH(2)	OH(4)	OH(6)	H	H	OH(6′)
Anthocyanidins	Cyanidin	OH	OH	OH	OH	OH	H

Hydrogen-Atom Transfer

$$H_nAntiox + {}^{\bullet}R \rightarrow H_{n-1}Antiox^{\bullet} + HR. \quad 1.$$

The important role of HAT in the antioxidant activity of chemical compounds has been well documented. Indeed, it has been proposed as a key reaction mechanism for polyphenols in general (Cao et al. 2014) and for several particular compounds of the polyphenol family, including procyanidins (Mendoza-Wilson et al. 2014), some hydroxychalcones (Xue et al. 2012), α-mangostin (Martínez et al. 2011), capsaicin (Galano & Martínez 2012), fisetin (Dimitrić Marković et al. 2014), orientin (Praveena et al. 2014), and cynarine and chlorogenic acids (Mikulski et al. 2014). HAT has also been found as an important free radical–scavenging mechanism for nonphenolic compounds such as glutathione (Galano & Alvarez-Idaboy 2011), lipoic and dihydrolipoic acids (Castañeda-Arriaga & Alvarez-Idaboy 2014), and tryptophan and its derivatives (Farmanzadeh & Najafi 2013). However, it is noteworthy that there are other reaction mechanisms yielding the same products as HAT, and properly differentiating among them can be a complex task.

Proton-Coupled Electron Transfer

PCET reactions yield exactly the same products as HAT and they can be globally represented by the reaction illustrated in Equation 1. The differences between the two mechanisms, PCET and HAT, can be clarified at the molecular level. Whereas in HAT the proton and the electron are transferred together as a single entity (a hydrogen atom), in PCET the electron and the proton are concertedly transferred in a single step as two separated particles (an electron and a proton). PCET is frequently described as a reaction in which a proton and an electron are transferred from different sets of orbitals, and theoretical chemistry is used to differentiate between this and the HAT mechanism. There are several strategies for that purpose, including the orientation of the single occupied molecular orbital (SOMO) density surfaces in the transition states, the electron-proton nonadiabaticity, and the topographical characteristics of the potential energy surfaces (Mayer et al. 2002, Sirjoosingh & Hammes-Schiffer 2011, Tishchenko et al. 2008). PCET has been proposed as a crucial mechanism in the antioxidant activity of flavonoids (Amić et al. 2014), the quinone-hydroquinone system (Nakayama & Uno 2010), eupatilin (Li et al. 2013), and diarylamines (Hanthorn et al. 2012).

Radical Adduct Formation

$$H_nAntiox + {}^{\bullet}R \rightarrow [H_nAntiox\text{-}R]^{\bullet}. \quad 2.$$

The key antioxidant structural feature in this case is the presence of multiple bonds, albeit electrophilic radicals are more likely to be involved in RAF reactions than nonelectrophilic radicals. Steric effects may also limit the viability of RAF reactions. This mechanism has been identified to be important for the free radical–scavenging activity of several antioxidants, including carotenoids (Liebler & McClure 1996), gentisic acid (Joshi et al. 2012), rebamipide (Sakurai et al. 2004), and hydroxybenzyl alcohols (Dhiman et al. 2009).

Single Electron Transfer

This mechanism can take place following two different pathways:

$$H_nAntiox + {}^{\bullet}R \rightarrow H_nAntiox^{+\bullet} + R^{-} \quad 3.$$

and

$$H_nAntiox + {}^{\bullet}R \rightarrow H_nAntiox^{+-\bullet} + R^{+}. \quad 4.$$

Equation 3 has been described as important for the free radical–scavenging activity of the enol isomer of curcumin (Barzegar 2012) and for the reactions of carotenoids with $^{\bullet}NO_2$ (Everett et al. 1995, Mortensen et al. 1997) and $CCl_3OO^{\bullet}$ (Hill et al. 1995), catechin analogs with peroxyl radicals ($ROO^{\bullet}$) (Nakanishi et al. 2004), edaravone derivatives with $^{\bullet}OH$, $^{\bullet}OCCl_3$, and $CH_3COO^{\bullet}$ (Pérez-González & Galano 2012), and resveratrol with oxygen radicals (Nakanishi et al. 2007). However, the second pathway (Equation 4) is involved in the reactions of the superoxide radical anion ($O_2^{\bullet -}$) with xanthones (Martínez et al. 2012) and carotenoids (Galano et al. 2010), and in the reactions of the NO radical with Trolox, caffeic acid, uric acid, and genistein (Sueishi et al. 2011). The relative importance of the second pathway increases with the electron donor capabilities of the reacting free radical.

Sequential Proton-Loss Electron Transfer

SPLET was first proposed by Litwinienko & Ingold (2003) and is currently associated with the free radical–scavenging activity of a vast number of antioxidants. It can be represented as:

$$H_nAntiox \rightarrow H_{n-1}Antiox^{-} + H^{+}. \quad 5.$$

$$H_{n-1}Antiox^{-} + {}^{\bullet}R \rightarrow H_{n-1}Antiox^{\bullet} + R^{-}. \quad 6.$$

At present, there is an overwhelming, and still increasing, amount of evidence supporting the key role of this mechanism on the protection against oxidative damage. SPLET has been identified as a crucial mechanism in the scavenging activity exerted by numerous compounds in polar environments. Some examples are Trolox (Alberto et al. 2013), curcumin (Litwinienko & Ingold 2004), vitamin E (Musialik & Litwinienko 2005), quercetin and epicatechin (Di Meo et al. 2013), piceatannol (Cordova-Gomez et al. 2013), resveratrol (Iuga et al. 2012), kaempferol (Dimitrić Marković et al. 2014), esculetin (Medina et al. 2014a), fraxetin (Medina et al. 2014b), morin (Marković et al. 2012b), hydroxybenzoic and dihydroxybenzoic acids (Fifen et al. 2011, Pérez-González et al. 2014), flavonoids (Musialik et al. 2009), isoflavonoids (Lengyel et al. 2013), xanthones (Martínez et al. 2012), procyanidins (Mendoza-Wilson et al. 2014), edaravone and its derivatives (Pérez-González & Galano 2012), gallic acid (Dorović et al. 2014), and erodiol (Marković et al. 2013b), among many others.

Sequential Electron Proton Transfer

SEPT is also a two-step mechanism involving both electron transfer and deprotonation, but in a different order than in the SPLET route:

$$H_nAntiox + {}^{\bullet}R \rightarrow H_{n-1}Antiox^{\bullet +} + R^{-}. \quad 7.$$

$$H_{n-1}Antiox^{\bullet +} \rightarrow H_{n-1}Antiox^{\bullet} + H^{+}. \quad 8.$$

SEPT has been identified as the main radical-scavenging route for vitamin E models when reacting with DPPH and galvinoxyl (Nakanishi et al. 2005) and for α-tocopherol when scavenging the theroxyl radical (Ouchi et al. 2009). SEPT has also been reported as important for the antioxidant

ability of baicalein (Marković et al. 2012a) and astaxanthin and its *n*-octanoic monoester and diester (Focsan et al. 2014), as well as for quercetin when it is in the presence of bases with HOMO energies lower than that of the SOMO of quercetin's radical cation (Marković et al. 2013a).

Sequential Proton-Loss Hydrogen-Atom Transfer

SPLHAT involves the deprotonation of the antioxidant, followed by an H transfer reaction:

$$H_nAntiox \rightarrow H_{n-1}Antiox^- + H^+. \quad 9.$$

$$H_{n-1}Antiox^- + {}^\bullet R \rightarrow H_{n-2}Antiox^{\bullet -} + HR. \quad 10.$$

There are several investigations demonstrating that the SPLHAT route plays an important role in the antioxidant activity of anthocyanidins (Estévez et al. 2010): in the reaction of gallic acid with $^\bullet OH$ (Marino et al. 2014), in esculetin when scavenging $^\bullet OOCH_3$ and a model of lipid peroxyl ($^\bullet OOCHCH_2$) radicals (Medina et al. 2014b), and in the free radical–scavenging activities of ellagic acid (Galano et al. 2014a), α-mangostin (Martínez et al. 2011), and propyl gallate (Medina et al. 2013).

However, the action of Type II antioxidants against free radicals depends on their ability to inhibit the endogenous production of oxidants. This becomes particularly important when the involved radical is a hydroxyl ($^\bullet OH$) because it is the most reactive and electrophilic of the oxygen-centered radicals. $^\bullet OH$ has been identified as the main free radical responsible for tissue and DNA damage. Therefore, inhibiting $^\bullet OH$ production is of primary importance in reducing OS.

The main intracellular sources of $^\bullet OH$ are the Fenton reaction and the metal catalyzed Haber-Weiss recombination (HWR). The most likely metal ions that are involved in such processes are Fe and Cu. The Fenton reaction involves their reduced forms:

$$Fe(II) + H_2O_2 \rightarrow Fe(III) + OH^- + {}^\bullet OH \quad 11.$$

and

$$Cu(I) + H_2O_2 \rightarrow Cu(II) + H^- + {}^\bullet OH. \quad 12.$$

The HWR, catalyzed by metal ions, can be written as:

$$Fe(III) + O_2{}^{\bullet -} \rightarrow Fe(II) + O_2 \quad 13.$$

and

$$Cu(II) + O_2{}^{\bullet -} \rightarrow Cu(I) + O_2 \quad \text{(Fenton)}. \quad 14.$$

It should be noted that the catalyzed HWR is the one with physiological importance because the noncatalyzed process is too slow (Weinstein & Bielski 1979).

Because the catalyst oxidized forms, Fe(III) and Cu(II), are the most abundant and stable species in biological media, the relative importance of the HWR is expected to be higher than that of the direct Fenton reaction. Therefore, under such conditions, the reduction process, Fe(III) to Fe(II) or Cu(II) to Cu(I), is the crucial step for the $^\bullet OH$ production. Accordingly, chelating agents able to decrease the viability of Fe(III) and Cu(II) reduction reactions are expected to be effective for preventing or inhibiting OS by limiting the $^\bullet OH$ production. Some examples of antioxidants able to exert their protection are ellagic acid (Galano et al. 2014a), melatonin and its metabolites

N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and cyclic 3-hydroxymelatonin (3OHM) (Galano et al. 2014b), quercetin (Leopoldini et al. 2006), and luteolin (Primikyri et al. 2015).

FREE RADICALS

From a chemical point of view, free radicals are species containing one or more unpaired electrons. This particular characteristic is responsible for their high reactivity and triggering chain reaction mechanisms. Most of the radicals found in vivo are reactive oxygen species (ROS) or reactive nitrogen species (RNS). The ROS are oxygen-centered free radicals, including the superoxide radical anion ($O_2^{\bullet-}$), hydroxyl ($^{\bullet}OH$), alkoxyl ($RO^{\bullet}$), $ROO^{\bullet}$, and hydroperoxyl ($HOO^{\bullet}$) radicals. The RNS are nitrogen-based radicals, including peroxynitrite ($ONOO^-$), nitric oxide ($NO^{\bullet}$), and nitrogen dioxide ($NO_2^{\bullet}$).

Among the oxygen-centered radicals, $^{\bullet}OH$ is the most electrophilic (Pryor 1988) and reactive, with a half-life of $\sim 10^{-9}$ s. It can react through a wide variety of mechanisms, and its reactions with a large variety of chemical compounds take place at, or close to, diffusion-controlled rates (rate constants $\geq 10^9$ M/s). It has been estimated that $^{\bullet}OH$ is responsible for 60% to 70% of the tissue damage caused by ionizing radiations (Vijayalaxmi et al. 2004). $^{\bullet}OH$ is so reactive that it is capable of immediately reacting, after formation, with almost any molecule in its vicinity, with little selectivity toward the various possible sites of attack. It has been held responsible for most important oxidative damage to DNA (Chatgilialoglu et al. 2009).

With respect to $^{\bullet}OH$, $ROO^{\bullet}$ are a less reactive species, capable of diffusing to remote cellular locations. Their half-lives are on the order of seconds (Pryor 1986), and their electrophilicity is significantly lower than that of $^{\bullet}OH$ (Pryor 1988). However, $ROO^{\bullet}$ can also react with other chemical species through different mechanisms. $ROO^{\bullet}$ are, in general, less reactive than $HOO^{\bullet}$ when R is an alkyl or an alkenyl group (Galano 2011). However, if R is a more efficient electron-accepting group, such as CCl_3, the reactivity of $ROO^{\bullet}$ toward organic molecules significantly increases. Indeed, the rate constants for the electron-transfer reactions involving $ROO^{\bullet}$ strongly depend on the chemical nature of R. The rate constant significantly increases with the electron-withdrawing character of the substituents. (Neta et al. 1989). $RO^{\bullet}$ radicals are formed from the reduction of peroxides and are significantly more reactive than $ROO^{\bullet}$ radicals, provided that R is the same in both species, but they are less reactive than $^{\bullet}OH$ (León-Carmona & Galano 2011).

As regards the RNS, the chemical reactivity of $NO^{\bullet}$ is rather limited, and consequently its direct toxicity is less than that of ROS (Squadrito & Pryor 1998). However, it reacts with $O_2^{\bullet-}$, yielding peroxynitrite (Radi et al. 2001), which is a very damaging species, as it is able to react with proteins, lipids, and DNA (Douki & Cadet 1996, Koppal et al. 1999). Nitrogen dioxide is a moderate oxidant, and its reactivity is somewhere between those of $NO^{\bullet}$ and $ONOO^-$ (Yan et al. 2014). NO_2 reacts with organic molecules at rates ranging from $\sim 10^4$ to 10^6 M/s, depending on the pH (Prütz et al. 1985).

INTRINSIC PROPERTIES OF THE ANTIOXIDANTS

The geometrical and electronic features of polyphenolic systems determine their antioxidant activity. In fact, when an antioxidant (A) interacts with a very reactive radical (R•) it becomes a radical itself (A•), giving rise to harmless species (RH). Only if the formed radical A• is less reactive, and thus more stable, than the initial one is the beneficial action of such compounds achieved. The essential structure of the natural phenolic antioxidants makes them able to extend the conjugation

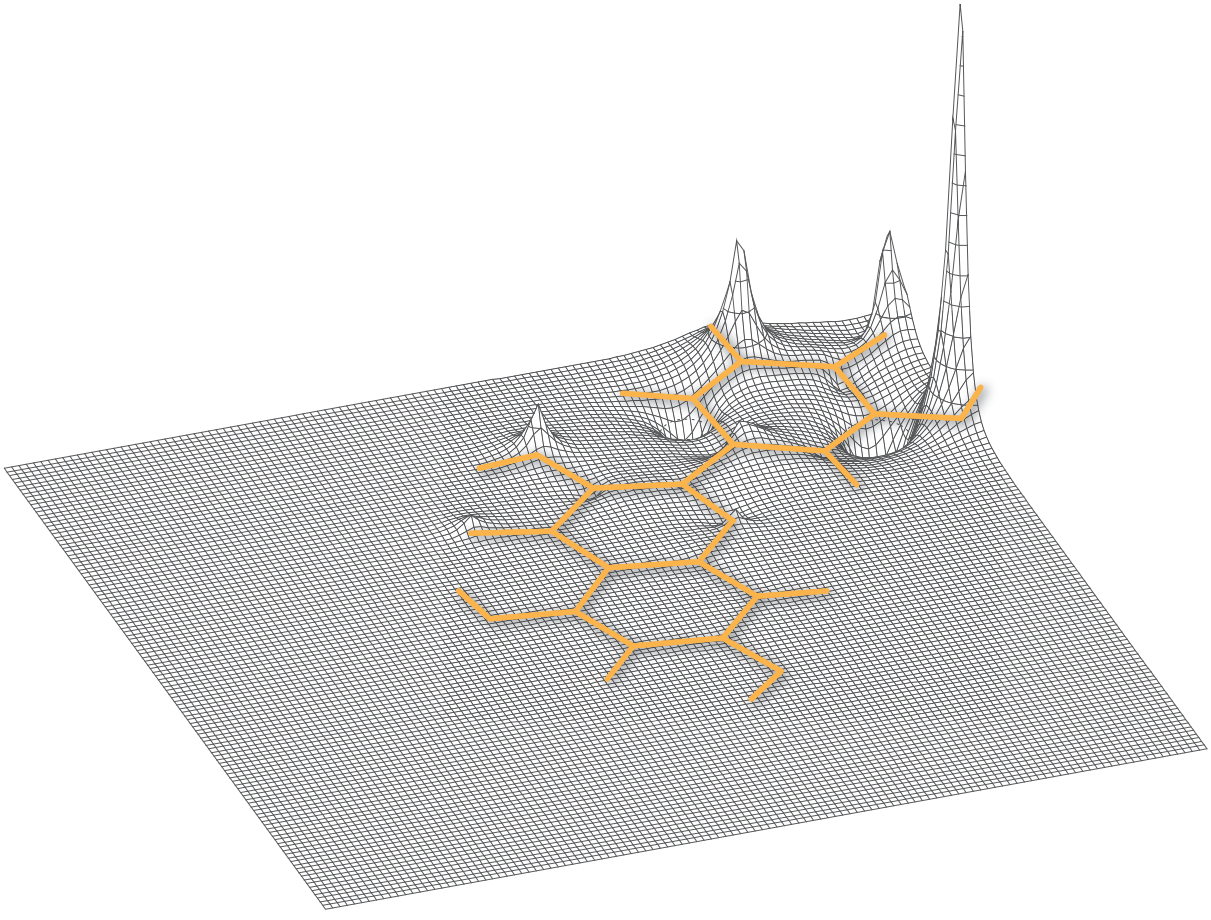
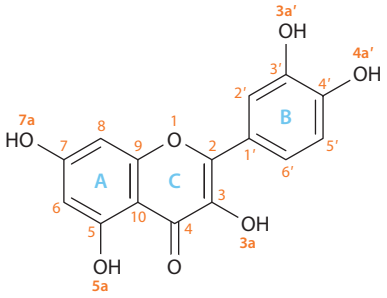


Figure 2

Electron spin density of the most stable radical (4a′) of quercetin computed in the gas phase at the M05-2X/6-311+G(d,p) level of theory.

upon the radicalization process (Leopoldini et al. 2011b). In this way, the obtained radical A• is highly stable and therefore largely unreactive. As shown in **Figure 2**, the radical obtained by the abstraction of a hydrogen atom from the 4a′ position on the B ring (see **Figure 3**) is characterized by a distribution of the spin density on the whole B ring and part of the central C ring; it is not concentered on the radicalized oxygen atom.

In most of the proposed antioxidant working mechanisms, a hydrogen, an electron, or their mixing is involved. In the first instance, the ability of a molecule to act as an antioxidant can be predicted by computing some of their intrinsic properties: bond dissociation enthalpies (BDEs), adiabatic ionization potentials (IPs), O-H dissociation enthalpies (PDEs), proton affinities (PAs) and electron transfer enthalpies (ETEs). In fact, in the HAT mechanism, in which a hydrogen atom from an OH group is transferred during the reaction, a lower BDE is associated with an easier dissociation of the phenolic O-H bond and, consequently, with a faster hydrogen transfer. In the SET mechanism, a lower IP is mandatory for the electron transfer from the antioxidant to the involved radical. In order to establish which exchange-correlation (XC) functional gives



Quercetin

Figure 3

Structure and numbering of quercetin.

the most reliable results we have done a benchmark on the simplest phenol system. Results are collected in **Table 2**.

Looking at BDEs, it can be observed that all the employed XC functionals give values (in benzene environment) that fall in a maximum deviation of 5 kcal/mol with respect to the experimental data (Lucarini & Pedulli 2010) in the same solvent. The better agreement is obtained with M05-2X, M06-2X, and B2PLYPD functionals with the former that reach an excellent agreement with the experimental counterpart (87.6 versus 87.2 kcal/mol).

Table 2 Bond dissociation enthalpies (BDEs), O-H proton dissociation enthalpies (PDEs), and electron transfer enthalpies (ETEs) computed at different levels of theory by using 6-311+G(d,p) basis set in benzene[a]

	BDE	PDE	ETE	IP	PA
B3LYP	82.9	239	82	161 (193)	319 (347)
B3LYPD	83.2	240	82	161 (193)	319 (347)
BP86	84.4	239	84	161 (193)	316 (344)
BP86D	84.8	239	84	161 (193)	316 (344)
B97D	82.1	243	80	157 (189)	320 (347)
TPSSh	83.1	241	79	158 (190)	320 (348)
PBE0	83.4	239	81	161 (192)	319 (348)
M05-2X	87.6	238	85	165 (194)	318 (345)
M06-2X	88.4	238	85	165 (195)	319 (345)
M06	84.1	239	83	161 (193)	317 (346)
MPWB1K	85.8	239	79	161 (193)	321 (350)
WB97XD	84.6	241	81	161 (193)	321 (350)
B2PLYP	86.0	240	82	161 (193)	319 (347)
B2PLYPD	86.2	240	82	161 (193)	319 (347)
Experimental	87.2[b]			(196)[c]	(347.5)[d]

[a]Adiabatic ionization potentials (IPs) and proton affinities (PAs) are computed in benzene and in vacuo (in parentheses). The available experimental values are reported for comparison. All energies are in kcal/mol.
[b]Lucarini & Pedulli 2010.
[c]Lipert & Colson 1990.
[d]Angel & Ervin 2004.

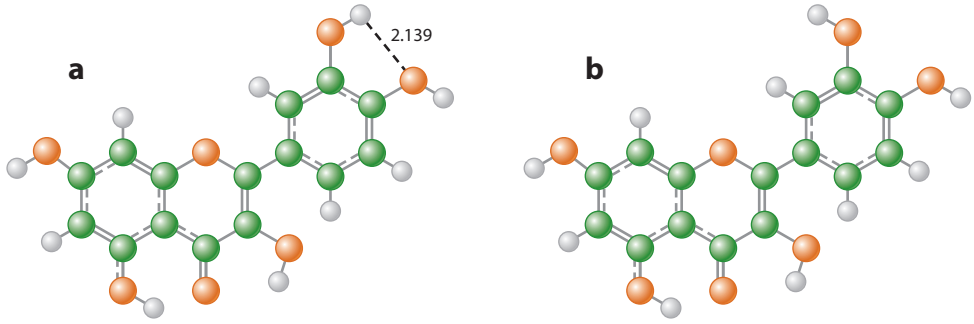


Figure 4

M05-2X/6-311+G(d,p) optimized structures of quercetin conformers (*a*) with and (*b*) without an H bond between 3′ and 4′ OH groups.

Because IP and PA values have been measured in the gas phase (Angel & Ervin 2004, Lipert & Colson 1990), we have reported both parameters computed in vacuo and in benzene in order to evaluate the effect of the solvent on these two properties. Also for IP values, the best agreement between theory and experiment is achieved by using the M05-2X and M06-2X functionals, with a deviation from the experimental value of only 2 and 1 kcal/mol, respectively. Regarding the PA, all the employed XC functionals seem to reproduce the gas-phase experimental data with an average error of less than 1 kcal/mol. From results obtained by this benchmark as well as considering previous experiences (Chiodo et al. 2010; Leopoldini et al. 2004a,b, 2007, 2011b), the M05-2X functional has been used for the other computation. Some intrinsic properties, especially the BDE, are sensitive to the topology around the O-H group. In particular, as previously evidenced (Leopoldini et al. 2010, 2011a; Mazzone et al. 2013a,b, 2015), the presence of other closer groups that allow the formation of hydrogen bonds reduces the BDE. The amount of this reduction has been evaluated on one of the most potent antioxidants, quercetin (see **Figure 3**), in which the spatial disposition of the OH groups in positions 3′ and 4′ of the B ring gives rise to two structures reported in **Figure 4**.

The first conformer (**Figure 4*a***) is obviously the most stable one and its structure is characterized by a hydrogen bond between H and O atoms of the OH group in 3′ and 4′ positions, respectively. Conformer b lies 4.3 kcal/mol above the energy of conformer a, and its topology does not include the hydrogen bond. The energy difference between the two structures accounts for the energetic stabilization due to the H-bond presence. The abstraction of 4a′ hydrogen in the two considered conformers requires 77.6 and 80.6 kcal/mol to occur, respectively. Therefore, the presence of the H bond reduces by 3 kcal/mol the BDE, facilitating a possible HAT mechanism.

Often in polyphenols more than one OH group is present on A, B, and C rings. In these cases, a preliminary study on the preferred O-H bond breaking is needed and the different BDEs must be computed. For example, quercetin includes in its structure two, two, and one OH groups on the A, B, and C rings, respectively (see **Figure 3**). Results computed in vacuo, collected in **Table 3**, show that the lower BDE occurs for the radicalization of 4a′ center (77.6 kcal/mol) followed by the 3a′ one (80.3 kcal/mol), whereas the highest value is found for the H abstraction by OH group in 5a position (101.5 kcal/mol) of the A ring.

The rationalization of these data can be fulfilled taking into account different structural and electronic factors, such as the delocalization and the spin distribution in the radicalized species, the intramolecular hydrogen bonds and the planarity. The difference in BDEs between the H abstraction from OH groups in 4a′ and 5a positions can be explained looking at the spin distribution

Table 3 Bond dissociation enthalpies (BDEs) for quercetin's radicals in vacuo, water, and pentylethanoate computed at the M05-2X/6-311+G(d,p) level of theory[a]

	In vacuo	Water	Pentylethanoate
3a	86.2	83.7	84.3
3a′	80.3	85.0	81.3
4a′	77.6	83.4	79.5
5a	101.5	95.3	98.2
7a	93.8	95.4	93.3

[a]All values are in kcal/mol.

of the unpaired electron in the radicalized species. Indeed, although in both cases the structure could be stabilized by several H bonds, in the 5a radical the unpaired electron is localized on the radicalization site, as the presence of the –C = O and –O– moieties on the C ring obstructs the spin distribution.

We conclude this section showing how, from the computed BDEs and IPs, some qualitative indication about the antioxidant ability and a suggestion of the preferred working mechanism can be extracted. **Table 4** reports the computed IP and BDE values, associated to the most stable radical, for a series of compounds with well-known radical scavenging activity.

It is noteworthy that the electron transfer mechanism, for which the IPs could be an indication, requires a higher amount of energy to take place than does the HAT mechanism. Among the studied systems, although the H abstraction is easier in gallic acid than in *trans*-resveratrol, the latter is the best suited to give an electron to a free radical, especially with respect to gallic acid. Therefore, the ability of a compound to lose an H is not strictly related to its ability to be ionized.

CHELATING ABILITY

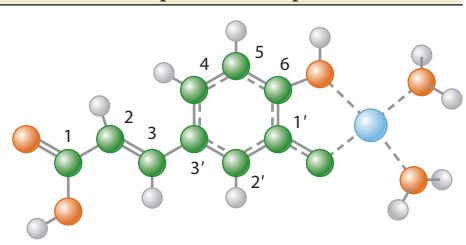
The chelating ability of an antioxidant against a series of metal ions contributes to reducing the viability of these ions [especially Fe(III) and Cu(II) naturally present in the cells], preventing or inhibiting OS by limiting •OH production. The majority of natural antioxidants contain OH as well as C=O groups and, consequently, could be good ligands able to bind transition metal ions. When the antioxidants possess different chelating sites, a careful investigation of the metalation process is mandatory. As an example, we report the study of the complexation process of the hydrated complex of Cu(II), $[Cu(H_2O)_4]^{2+}$ with caffeic acid considering the 1:1 stoichiometric ratio. All the possible chelation sites of caffeic acid have been explored, as well as the different chelation routes, i.e., the direct chelation and the deprotonation-chelation mechanisms. Results

Table 4 Bond dissociation enthalpies (BDEs) and adiabatic ionization potentials (IPs) for selected antioxidant compounds computed at the M05-2X/6-311+G(d,p) level of theory in benzene[a]

	BDE	IP
Caffeic acid	78.8	157
Gallic acid	78.1	163
Trolox	78.5	147
Quercetin	79.4	150
Trans-resveratrol	82.5	145

[a]All values are in kcal/mol.

Table 5 Gibbs free energies (ΔG, kcal/mol) for the chelation reaction at different binding sites, in aqueous solution computed at M05/6-31+G(d) at 298.15 K[a]

Binding site	ΔG	Most probable complex
3_H-4_H	0.3	
3-4_H	−23.3	
3_H-4	−19.1	
$3'_H$	−1.4	
3′	−19.2	

[a]H atoms are removed from the OH binding sites unless denoted with a subscript H.

reported in **Table 5** show that the direct complexation of neutral caffeic acid, in which all the OH groups are not deprotonated, leads to the formation of unstable complexes. The most stable predicted complex is that in which the copper ion binds the deprotonated oxygen in the 3 position and the lone pair of the hydroxyl oxygen in the 4 position. The stabilization of the most probable complex, calculated with respect to sum of energies of the reactants, is found to be 23.3 kcal/mol. In a range of approximately 5 kcal/mol, another two coordination sites are equally possible. The stabilization of Cu(II) complexes with caffeic acid indicates the ability of such an antioxidant to bind a metal ion, limiting •OH production and preventing OS.

KINETICS

Rate constants are a very useful criterion to establish trends in reactivity and thus to identify the most efficient compounds for scavenging free radicals: the faster the reaction the higher the primary antioxidant activity. Recently, a computational protocol has been proposed for that purpose. It is known as the quantum mechanics–based test for overall free-radical scavenging activity (QM-ORSA) (Galano & Alvarez-Idaboy 2013). This protocol is based on the following methodological aspects:

- Always using the same computational methodology
- Modeling all mechanisms and reaction sites
- Modeling reactions with the same free radical
- Using the transition state theory (TST) for calculating the rate constants of each HT and RAF reaction channel
- Using the Marcus Theory to estimate the reaction barriers involving electron transfer
- Taking into account the reaction path degeneracy
- Including tunneling corrections
- Using 1 M standard state
- Taking into account the solvent cage effects
- Correcting for diffusion-controlled rates
- Calculating total rate coefficients and branching ratios
- Calculating overall rate coefficients
- Using a threshold value to identify compounds with significant primary AOC
- Making separated comparisons for nonpolar and polar environments
- Establishing trends

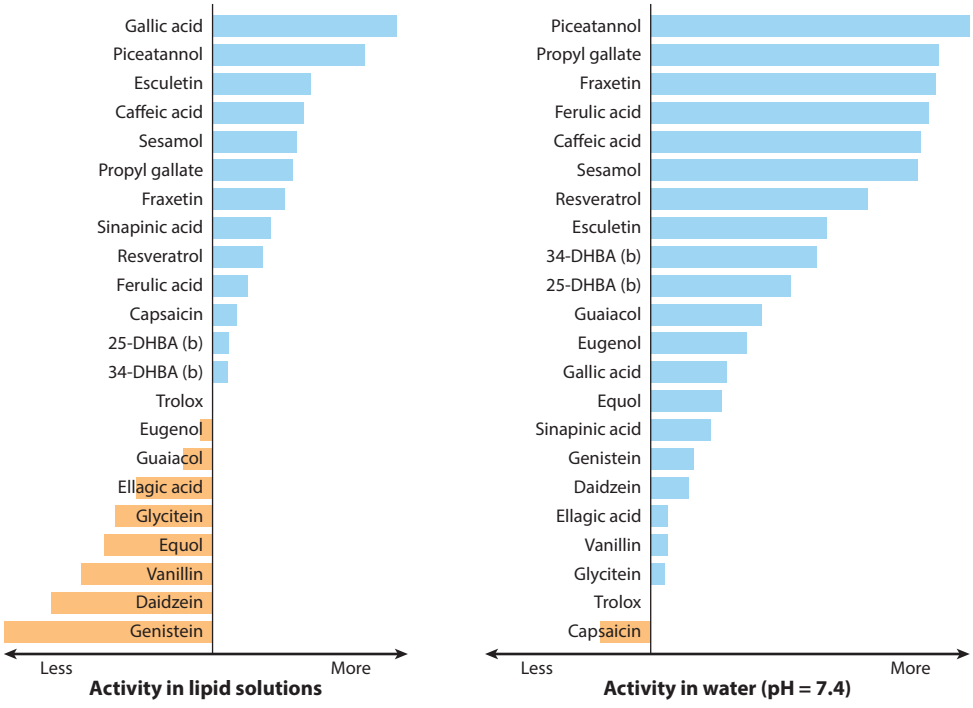


Figure 5

Trends in activity for phenolic compounds in lipid (*left*) and aqueous (*right*) solutions. The bar lengths are proportional to the activity, using Trolox as a reference. Data from Caicedo et al. 2014; Cordova-Gomez et al. 2013; Galano et al. 2011a,b, 2012, 2014a; Galano & Martínez 2012; Galano & Pérez-González 2012; Iuga et al. 2012; León-Carmona et al. 2012; Medina et al. 2013, 2014a,b; Pérez-González et al. 2014. Abbreviation: DHBA, dihydroxybenzoic acid.

The analyses based on this protocol can be performed using two different scales (the absolute, based on overall rate coefficients, and the relative, using Trolox as a reference). Using this strategy, we present the trend in antioxidant activity for some phenolic compounds in nonpolar and aqueous solutions (**Figure 5**).

This figure also shows the important role of the environment's polarity on the reactivity of phenolic compounds toward free radicals. In an aqueous solution, the activity is increased, mainly because such an environment promotes deprotonation, which allows the SPLET mechanism to contribute to the overall free-radical scavenging activity of these compounds. In addition, in an aqueous solution most of the analyzed compounds are more efficient than Trolox for that purpose, whereas in lipid media approximately one third of them are less efficient than the reference compound.

SUMMARY POINTS

1. Bond dissociation enthalpies, adiabatic ionization potentials, and proton affinities are reliably predicted, and their value can give initial information on the scavenging mechanism against radicals.

2. The determination of the potential energy surface is important to establish the main mechanism involved in the antioxidant activity of a given chemical compound.
3. The antioxidant chelation power allows the reduction of the bioavailability of metal ions that can act as sources of radicals throughout Fenton reactions.
4. Kinetic constants are accurately reproduced and can be used as absolute and relative criteria to establish trends in antioxidant activities.
5. Solvent effects should be taken into account; thus, their influence on the antioxidant activity can be elucidated.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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