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The triple defensive barrier of phenolic compounds against the lipid oxidation-induced damage in food products

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Abstract

Background: Although prooxidant activities have also been described, phenolic compounds can act as chelating and free radical scavengers. These protective functions would be their first and second defense barriers against the lipid-induced damage in foods. In addition, recent studies have shown that they can act as lipid-derived carbonyl scavengers, therefore avoiding that these toxic and very reactive compounds can modify essential food components such as aminophospholipids, amino acids, and proteins. These results point out to phenolic compounds also as responsible for a third defense barrier against the lipid oxidation-induced damage in foods.

Scope and approach: This review collects the scattered information existing on the role of phenolic compounds as lipid-derived carbonyl scavengers and introduces a general lipid oxidation scheme in which the triple function of phenolic compounds can be clearly understood by pointing out where they are acting as a function of their structure.

Key findings and conclusions: The structural requirements for the three barriers are different and phenolic compounds are suggested to be classified into seven groups as a function of the number and kind(s) of function(s) exhibited. This better classification and understanding of how different phenolic compounds protect foods will help to the food industry to employ the most appropriate phenolic compounds in each formulation and will also contribute to better understand the biological functions of these compounds.

Keywords

Carbonyl-scavenging ability; Lipid-derived reactive carbonyls; Lipid oxidation; Phenolic compounds; Structure-activity relationship

1. Introduction

Lipid oxidation is a major food problem because it causes consumer rejection and potential safety problems. Thus, it is responsible for the deterioration of polyunsaturated lipids and produces changes in flavor, texture, appearance, and nutritional quality in food products (Waraho, McClemens, & Decker, 2011). This traditional problem in the food industry has got worse in recent years because of the removal of hydrogenated fats, the addition of more unsaturated fatty acids to improve nutritional content, and the consumer desire to remove synthetic food additives including antioxidants. Because of that, the search of satisfactory strategies for inhibiting lipid oxidation has been (and still is) a constant for the food industry.

The assayed strategies have included the use of both primary antioxidants (those that disrupt the oxidative free radical chain reaction) and secondary antioxidants (those that prevent lipid oxidation by deactivating singlet oxygen, chelating metal ions, absorbing ultraviolet radiation, scavenging oxygen, or helping to regenerate primary antioxidants) (Senanayake, 2013). Among the different compounds assayed, natural phenolic compounds have been shown to effectively scavenge free radicals and to chelate transition metals, thus stopping progressive autoxidative damage and production of off-odours and off-tastes (Brewer, 2011). In addition, phenolic compounds are also able to scavenge the carbonyl compounds produced in the lipid oxidation pathway, providing in this way an additional protection to foods against the consequences of lipid oxidation. On the other hand, prooxidant activities of phenolic compounds have also been described (Chedea, Choueiri, Jisaka & Kefalas, 2012; Halliwell, 2008; Masuda, Inai, Miura, Masuda, & Yamauchi, 2013), although they will not be discussed in depth in the present review.

63 The main purpose of this review is to collect the scattered information existing on the
64 role of phenolic compounds as lipid-derived carbonyl scavengers, and to elaborate a
65 general scheme of lipid oxidation in which the different functions of phenolic
66 compounds in the protection of lipid oxidation consequences (as chelating agents, as
67 free radical scavengers and as carbonyl trapping agents) can be easily understood.

68 **2. The lipid oxidation pathway as a source of both free radicals and carbonyl**
69 **compounds**

70 Lipid oxidation is a free radical chain reaction that proceeds through the common
71 stages of initiation, propagation and termination (Schaich, 2013). However, many of the
72 secondary and tertiary products formed by free radical reactions are very reactive and
73 react covalently with the surrounding food components, therefore extending lipid
74 oxidation consequences (Zamora & Hidalgo, 2005).

75 The generation of primary free radicals is a thermodynamically unfavorable reaction
76 and needs to be facilitated by the presence of oxidation initiators such as light, heat,
77 ionizing radiation, transition metals, metalloproteins, oxidants, various hemolysis-prone
78 substances and enzymes (Senanayake, 2013). In any case, the result will be the
79 abstraction of a hydrogen atom from an unsaturated fatty acid and the formation of the
80 corresponding alkyl radical (equation 1).

81 $$LH + \text{initiator} \rightarrow L^{\bullet} \qquad (1)$$

82 In mixtures of acyl chains with different unsaturation degree, the abstracted proton is
83 usually a proton bonded to a doubly allylic carbon and the produced radical suffers then
84 a rearrangement to produce a conjugated diene system. The formed alkyl radical reacts
85 faster with oxygen than with lipids. Therefore the next step in the propagation reaction

is the formation of the corresponding peroxyl radical ($LOO^{\bullet}$). This is a reversible reaction because the peroxyl radical can suffer a β-elimination reaction to produce again the alkyl radical, although the produced rearrangements would not be reversed (equation 2).

$$L^{\bullet} + O_2 \leftrightarrow LOO^{\bullet} \quad (2)$$

This new radical is relatively slow to abstract an hydrogen from a new lipid molecule. Therefore, there is plenty of time for alternative reaction pathways that may compete and change the direction of the oxidation.

The reaction that continues the free radical chain is the hydrogen abstraction from a new lipid molecule (equation 3).

$$LOO^{\bullet} + LH \rightarrow LOOH + L^{\bullet} \quad (3)$$

However, when these new lipid molecules are not immediately available during oxidation, peroxyl radicals react by alternative pathways. The most facile pathway is addition to a neighboring double bond. If this double bond belongs to the same molecule (a *cis* double bond two carbons away from the peroxyl radical) a cyclic product (epidioxide radical) is formed. This new radical reacts rapidly with oxygen to produce the corresponding epidioxide peroxyl radical (equation 4).

$$LOO^{\bullet} \rightarrow \text{epidioxide radical} \rightarrow \text{epidioxide peroxyl radical} \quad (4)$$

If the carbon-carbon double bond belongs to a different molecule, a dimer is produced, which either can continue polymerizing afterwards or can produce monomeric products (epoxides).

Peroxyl radicals can also suffer a disproportionation reaction to produce alkoxyl radicals ($LO^{\bullet}$), although these last radicals are also produced by decomposition of lipid hydroperoxides (equation 5).

$$LOOH \rightarrow LO^{\bullet} + OH^{\bullet} \quad (5)$$

$LO^{\bullet}$ radicals are much more reactive than $LOO^{\bullet}$ by several orders of magnitude. This is the reason for the very rapid oxidation that takes place in the second stages of oxidation after a very slow oxidation in the induction period. This radical suffers a cascade of reactions including: hydrogen abstraction to continue the free radical chain at the same time that they are converted into alcohols; internal rearrangements to produce epoxides; addition to double bonds to produce polymerization; and scissions to produce a mixture of carbonyl compounds (aldehydes, ketones, keto-acids), fatty acids, alcohols, alkanes, and alkenes.

The favored pathways in this cascade of reactions are determined by the reaction conditions, the solvent, and the lipid concentration and conformation. In any case, it produces a complex mixture of products, some of which are stable but others are able to react with the surrounding food components, therefore broadcasting the oxidative damage from lipids to all kind of molecules. Among the different produced reactions, carbonyl-amine reactions are particularly important because they have been shown to produce important changes in foods with both positive and negative consequences (Hidalgo & Zamora, 2004; Zamora & Hidalgo, 2008; Zamora & Hidalgo, 2015). A detailed description of these reactions is out of the scope of this review and they have been described somewhere else (Hidalgo & Zamora, 2016; Zamora & Hidalgo, 2005).

3. The chelating ability of phenolic compounds

The first function of phenolic compounds as inhibitors of lipid oxidation is to chelate or to form complexes with the transition metal catalysts responsible for the initiation of lipid degradations. Many phenolics have a strong capacity for binding ferric ions due to the presence of iron-binding motifs (Kohkhar & Owusu Apenten, 2003). Fig. 1 shows the chemical structure of two major flavonoids: catechin and quercetin. The molecular structure of flavonoids consist of a benzopyran (rings A and C) and a phenyl ring (ring B), which have a hydroxylation pattern that is characteristic for each flavonoid. Their chelating ability depends on this hydroxylation pattern because flavonoids have a tendency to serve as hydrogen donors, which contributes to the formation of metal coordination complexes with good stability (Mira, Fernandez, Santos, Rocha, Florencio & Jennings, 2002). In addition, the structure of the complex formed depends on a number of factors, including the coordination number and oxidation state of the metal ion, the number and proximity of electron donors in the flavonoid, and the chelating conditions such as temperature and pH (Selvaraj, Krishnaswamy, Devashya, Sethuraman, & Krishnam, 2013). Although other complexes can also be produced, when the carbonyl group is available, commonly the metal ion complexes are preferentially formed between the keto group in the C-4 and the hydroxyl group in C-5, resulting in either 1:1 or 1:2 metal-flavonoid complexes. In the case of catechin, where the carbonyl group is absent, its ability to chelate cupric ions has been attributed to the presence of the catechol group in the B-ring (Mira, Fernandez, Santos, Rocha, Florencio & Jennings, 2002). These last hydroxyl groups have also been implied in the formation of 2:1 complexes between cupric ions and quercetin (Bukhari, Memon, Mahroof-Tahir, & Bhanger, 2009).

153 The complexation of the metal ions produces a special spatial orientation in the
154 flavonoid, which has been related to the pharmacological activity described for these
155 complexes. The biological activities described for flavonoid-metal ion complexes
156 include anti-inflammatory, anti-bacterial, anti-diabetic, anti-tumor, and antioxidant
157 activities both *in vitro* and *in vivo* (Selvaraj, Krishnaswamy, Devashya, Sethuraman, &
158 Krishnam, 2013).

159 On the other hand, combinations of antioxidants and metal ions generate reactive
160 oxygen species under *in vitro* conditions as shown by using electron spin resonance
161 (ESR) (Iwasaki, Oda, Tsukuda, Nagamori, Nakazawa, Ito, & Saito, 2014). Furthermore,
162 phenolics can reduce metal ions and result in increased oxidation (Kondakçi, Özyürek,
163 Güçlii, & Apak, 2013; Nkhili, Loonis, Mihai, El Hajji, & Dangles, 2014).

164 **4. The free radical-scavenging ability of phenolic compounds**

165 Phenolic compounds also delay the lipid oxidation process by scavenging the free
166 radicals that either initiate the lipid oxidation or take part in the propagation of the free
167 radical chain. This is consequence of their well-known ability of scavenging a wide
168 range of both reactive oxygen species (ROS) and reactive nitrogen species (RNS) such
169 as superoxide, hydroxyl, peroxyl, and alkoxyl radicals, and peroxynitrous and
170 hypochlorous acids (Maqsood, Benjakul, Abushelaibi, & Alam, 2014). The reaction is
171 produced by donation of a hydrogen atom to the radical at the same time that the
172 phenolic compound is converted into a phenolic free radical according to equation 6
173 (AH is the phenolic compound).

174 $$LOO^{\bullet} + AH \rightarrow LOOH + A^{\bullet} \qquad (5)$$

Differently to lipid radicals and other ROS and RNS, the produced phenolic radicals do not continue the free radical chain because this new radical is stabilized by electron delocalization throughout the phenolic ring(s).

The free radical-scavenging potential of phenolic compounds depends on the pattern (both number and location) of free hydroxyl groups in the flavonoid skeleton. This distribution seems to be more important than the flavanoid backbone alone. The hydroxyl configuration in the B-ring seems to be the most significant determinant of scavenging of both ROS and RNS (Heim, Tagliaferro, & Bobilya, 2002). When the catechol group is present at B-ring, a fairly stable *ortho*-semiquinone radical is formed that facilitates electron delocalization (Moya, Paya, Rios, & Alcaraz, 1990). Flavonoids lacking catechol or *o*-trihydroxyl (pyrogallol) systems form relatively unstable radicals and are weak scavengers (Pannala, Chan, O'Brien, & Rice-Evans, 2001).

The significance of other hydroxyl configurations is less clear, although the presence of a hydroxyl group at position 3 seems to increase antioxidant activity (flavonoid carbon numbering is shown in Fig. 1). This might be a consequence of the torsion angle of the B-ring with respect to the rest of the molecule. Flavonols and flavanols with a 3-OH are planar because of a hydrogen bond with the hydroxyl groups of B-ring, while the flavones and flavanones, lacking this feature, are slightly twisted (Acker, de Croot, van der Berg, Tromp, den Kelder, van der Vijgh, & Bast, 1996). Planarity permits conjugation, electron dislocation, and the corresponding increase in flavonoid phenoxyl radical stability.

Compared to the B-ring hydroxylation pattern, the impact of the A-ring arrangement on antioxidant activity is of questionable significance (Heim, Tagliaferro, & Bobilya,

198 2002). Furthermore, the closed C-ring does not seem to be critical to the activity of
199 flavonoids because chalcones are active antioxidants (Mathiesen, Malterud, & Sund,
200 1997).

201 **5. The carbonyl-scavenging ability of phenolic compounds**

202 When lipids are oxidized in the presence of other food components (e. g., proteins,
203 antioxidants, etc.), oxidative reactions can be terminated by reactions with compounds
204 other than those originating from oxidation of the lipid substrate. These last reactions
205 influence reaction rates and produce significant consequences in the color, flavor, and
206 texture of foods (Hidalgo & Zamora, 2000). Particularly, the carbonyl-amine reactions
207 initiated by lipid oxidation products has long been related to both the Maillard-like
208 reactions observed in many fatty foods during processing and storage (Hidalgo &
209 Zamora, 2016; Zamora & Hidalgo, 2005; Zamora & Hidalgo, 2015) and the progressive
210 accumulation of age-related yellow-brown pigments (lipofuscins) in man and animals
211 (Dazhong, 2015; Hidalgo & Zamora, 1993; Yin, 1996). Recent investigations also show
212 that phenolic compounds are also playing a role in these reactions.

213 To determine that the inhibition produced by phenolic compounds is related to
214 carbonyl trapping and not to free radical scavenging, it is essential to select a reaction
215 produced as a consequence of carbonyl chemistry. A reaction very appropriated in this
216 sense is the formation of the heterocyclic aromatic amine 2-amino-1-methyl-6-
217 phenylimidazo[4,5-*b*]pyridine (PhIP). PhP is formed in several steps, which are
218 schematically shown in Fig. 2. A more detailed description of the reaction mechanism
219 can be found in Zamora & Hidalgo (2015). The first step is the Strecker degradation of
220 phenylalanine to produce phenylacetaldehyde, a step that does not need the presence of
221 creati(ni)ne but it is facilitated in the presence of reactive carbonyl compounds derived

from carbohydrates (Rizzi, 2008; Yaylayan, 2003), lipids (Hidalgo & Zamora, 2004), amino acids (Hidalgo, Alcon, & Zamora, 2013), or polyphenols (Delgado, Zamora, & Hidalgo, 2015; Rizzi, 2006). The next step is the reaction of the formed phenylacetaldehyde with creati(ni)ne to produce the corresponding adduct (Zöchling & Murkovic, 2002), which has the basic structure of PhIP but it still needs the finishing of the pyridine ring with the inclusion of one carbon and one nitrogen atom. These atoms are finally incorporated by the formaldehyde and ammonia produced in the thermal decomposition of phenylalanine, phenylacetaldehyde and/or creati(ni)ne, or other food components (Zamora, Alcón & Hidalgo, 2014).

PhIP formation has been long known to be inhibited by phenolic compounds (Cheng, Chen, and Wang, 2007; Persson, Graziani, Ferracane, Fogliano, & Skog, 2003), but the inhibition of PhIP formation did not correlate with the antioxidant/free radical-scavenging capacity of the phenolic compounds responsible for its inhibition (Cheng, Chen, and Wang, 2007; Damasius, Venskutonis, Ferracane, & Fogliano, 2011). As observed in the above reaction mechanism, the reason for that is that there are not free radicals implied in PhIP formation. Therefore, the inhibition has to be produced by trapping of the carbonyl compounds involved in the formation of PhIP (phenylacetaldehyde, formaldehyde, and the carbonyl compounds responsible for phenylacetaldehyde formation) (Zamora & Hidalgo, 2015).

5.1. The carbonyl compounds scavenged by phenolic compounds

The carbonyl scavenging ability of phenolic compounds has been long known (Totlani & Peterson, 2005; Peng, Cheng, Ma, Chen, Ho, Lo, Chen, & Wang, 2008; Lo, Hsiao, & Chen, 2011), but it has been more recently when this ability, and not the free

radical scavenging, has been related to the protective effect of polyphenols in some biological processes such as the inhibition of the formation of advanced glycation end-products (AGEs) in the course of Maillard reaction (Peng, Ma, Chen, & Wang, 2011) and the control of Maillard-type off-flavor development in processed milk (Kokkinidou & Peterson, 2014). The reactive carbonyls mostly studied in this sense have been glyoxal and methylglyoxal (Lo, Li, Tan, Pan, Sang, & Ho, 2006; Sang, Shao, Bai, Lo, Yang, & Ho, 2007; Shao, Bai, He, Ho, Yang, & Sang, 2008; Liu & Gu, 2012; Navarro, Fiore, Fogliano, & Morales, 2015; Navarro, & Morales, 2015; Yoon, & Shim, 2015). In addition, the reaction between phenylacetaldehyde and phenols has also been studied, mostly in relation to the inhibition of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) formation exhibited by polyphenols (Cheng, Wong, Cho, Chu, Sze, Lo, Chen, & Wang, 2008; Cheng, Wong, Chao, Lo, Chen, Chu, Che, Ho, & Wang, 2009; Delgado, Hidalgo, & Zamora, 2016).

Although lesser studied than the highly reactive short dicarbonyl compounds glyoxal and methylglyoxal, lipid-derived reactive carbonyls have also been shown to be scavenged by phenolic compounds. The studied compounds have been alkanals (acetaldehyde and propanal), alkadienals (malondialdehyde), alkenals (acrolein, 2-pentenal, 2-octenal), and 4-hydroxy-2-nonenal (Zhu, Zheng, Cheng, Wu, Zhang, Tang, Sze, Chen, Chen, & Wang, 2009; Zhu, Liang, Cheng, Peng, Lo, Shahidi, Chen, Ho, & Wang, 2009; Hidalgo & Zamora, 2014; Delgado, Hidalgo, & Zamora, 2016), although unequivocal structures for the produced compounds were not always described.

5.2. Structure-activity of phenolic compounds for their carbonyl-scavenging ability

Analogously to the observed for the chelating and free radical-scavenging activities, the carbonyl trapping potential of phenolic compounds depends on the pattern (both number and location) of free hydroxyl groups. In a study analyzing the structure/activity relationship of phenolic compounds for the inhibition of PhIP formation, Salazar, Arambula-Villa, Hidalgo & Zamora (2014) found that phenols having two hydroxyl groups at *meta* positions of the aromatic ring were the most efficient inhibitors. The reason for that is that these isomers concentrate a high electronic density in some carbons and this electronic density is needed for the reaction with carbonyl compounds. The reaction is produced by addition of a phenolic carbon (or a hydroxyl group) to a carbon with a low electronic density in the carbonyl compound. Therefore, any substituent or substitution pattern that favors electron delocalization will produce a decrease in the carbonyl scavenging ability of phenolic compounds. This requirement is the contrary to that for a high free-radical scavenging activity in which a pattern that delocalizes the free electron is needed.

The positions with the highest electronic densities are the carbons at the α-position to the carbons with the hydroxyl group in the phenolic ring when there are two hydroxyl groups in *meta* positions. Thus, for the resorcinol shown in Fig. 3, the carbons with the highest electronic density are those at positions 2, 4, and 6. Analogously, the carbons with the highest electronic density in the quercetin (Fig. 3) are those at positions 6 and 8. However, not all these carbons have the same reactivity, although they have an analogous electronic density, because of steric hindrance. Thus, the most reactive carbons for the resorcinol shown in Fig. 3 are those at positions 4 and 6 (Hidalgo & Zamora, 2014), and the most reactive carbon for quercetine is the carbon at position 8 (Zamora, Aguilar, Granvogl, & Hidalgo, unpublished results).

In addition to the reactivity of the phenol, the positive charge in the carbonyl compound is also important and the most activated carbonyl compounds, such as glyoxal or methylglyoxal, can also react with less active carbons of the phenolic compound. The reactivity will be determined not only by the positive charge of the carbonyl carbon but also by the existence of either a delocalized system or steric hindrance. Thus, for example, the reaction of methylglyoxal involves the carbonyl carbon that is not linked to the methyl group (Sang, Shao, Bai, Lo, Yang, & Ho, 2007). In the case of 2-akenals, the reaction begins with an addition to the carbon-carbon double bond (Hidalgo & Zamora, 2014).

5.3. Chemical structures of the carbonyl-phenol adducts produced

The structure of the adduct produced depends on the carbonyl compound implied. Single carbonyls suffer the addition of the phenolic compound and the corresponding alcohol is produced (Fig. 3). Depending on the reaction conditions and both the carbonyl and the phenolic compound involved, the formed adduct can suffer then a dehydratation reaction to produce a more stable conjugated compound. An example of this dehydration has been observed in the reaction of phenylacetaldehyde with different flavonoids (Cheng, Wong, Cho, Chu, Sze, Lo, Chen, & Wang, 2008; Cheng, Wong, Chao, Lo, Chen, Chu, Che, Ho, & Wang, 2009). Figure 4 shows the structure of two adducts obtained in the reaction of phenylacetaldehyde with naringenin and norartocarpetin.

The reaction of phenolic compounds with 2-alkenals is more complex because both the carbonyl group and the conjugated carbon-carbon double bond are involved. In addition, the initial adducts produced suffer then a cyclization reaction to produce a

more stable heterocyclic structure (Hidalgo & Zamora, 2014). The produced reaction is shown in Fig. 5. Differently to the reaction with saturated aldehydes, the products of the addition of both the CH and the OH groups of the phenol to the carbonyl compound have been described. The adduct produced by the addition of the CH group to the aldehyde is relatively stable after formation of a hemiacetal structure. However, the adduct produced by the addition of the OH group to the aldehyde is unstable. In a first step, it produces a dehydrated compound, which has been isolated and characterized for a significant number of phenolic compounds (Hidalgo & Zamora, 2014). However, this first adduct has been shown to suffer further polymerizations which might also be related to the browning development in these reactions.

The reaction pathways responsible for the carbonyl scavenging of more complex lipid oxidation products remain to be elucidated because of the complexity of reaction mixtures. Thus, for example, in the reaction with 2,4-alkadienals, in addition to minor 2,4-alkadienal/phenol adducts, the formation of 2,4-alkadienal decomposition products and the adducts of these last compounds with the phenolic compounds have been observed (Hidalgo & Zamora, unpublished results). To this respect, the thermal degradation of lipid-derived aldehydes has been the objective of a recent study (Zamora, Navarro, Aguilar, & Hidalgo, 2015).

5.4. The beneficial effects of the produced carbonyl-phenol adducts

Analogously to the therapeutic uses of phenol-metal chelates described above, a couple of studies regarding to the potential health benefits of carbonyl-phenol adducts have recently appeared. Both studies analyzed the chemopreventive potential of the adducts formed between phenylacetaldehyde and flavonoids. In the first study, Li, Zhu,

Chen, Cheng, Zykova, Oi, Lubet, Bode, Wang, & Dong (2014) identified the adduct between naringenin and phenylacetaldehyde [(*E*)-5,7-dihydroxy-2-(4-hydroxyphenyl)-6-styrylchroman-4-one, Fig. 4] as a selective inhibitor of cyclooxygenase-1. This inhibition allowed that this compound effectively suppressed colorectal cancer growth in a 28-day colon cancer xenograft model without any obvious systemic toxicity. The inhibitory effect of the adduct has been related to the binding of the adduct to the cyclooxygenase-1 active site by forming three hydrogen bonds with Tyr355, Phe518, and Ser530.

In the second study, Zheng, Yan, Xia, Zhang, Wang, Chen, & Xu (2016) found that the adduct between phenylacetaldehyde and norartocarpetin [(*E*)-2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-8-styryl-4*H*-chromen-4-one, Fig. 4] significantly induced cancer cell death on three liver cancer cell lines HepG2, SMMC-7721 and QGY-7703. Authors concluded that the adduct had anticancer potential via intrinsic caspase-dependent and cell context-dependent MAPKs pathways.

6. The triple defensive barrier of phenolic compounds against the lipid oxidation-induced damage in food products

As described in section 2, the lipid oxidation pathway is a source of both free radicals and carbonyl compounds. It is schematically shown in Fig. 6. The lipid oxidation pathway is initiated by the abstraction of a proton in the lipid and the formation of the corresponding alkyl radical. This lipid radical enters in a free radical-propagation circle that finishes with the formation of the lipid hydroperoxide (LOOH). However, this is not a stable molecule, and it can be cleaved to produce alkoxyl and hydroxyl radicals. The free radical termination reactions are the conversion of alkoxyl radicals into stable molecules through three types of reactions: stabilization reactions to

produce compounds of analogous molecular weights to the original lipid; scission reactions to produce molecules of a molecular weight lower than the original lipid; and polymerization reactions to produce polymers of higher molecular weights than the initial lipid. Scission reactions include the formation of short chain volatile products with a high importance in the development of off-flavors as well as toxicity in foods (Guillen & Uriarte, 2012).

Although this is the end of the free radical part of the lipid oxidation process, their consequences are broadcasted because of the produced compounds. Some of them, in particular carbonyl compounds, are highly reactive and the consequences of the oxidation continue. These compounds react with amino compounds producing nonenzymatic browning and the formation of advanced lipoxidation end-products. The initial product formed between the carbonyl compound and the amino compound is the corresponding imine which can suffer again three kinds of reactions: stabilization reactions to produce the corresponding carbonyl-amine adducts of a molecular weight similar to the addition of the molecular weights of the reagents; scission reactions to produce volatile compounds; and polymerization reactions to produce the polymers responsible for the browning formation in these reactions. Different to the volatile compounds formed in the cleavage of alkoxyl radicals which have been related to rancid flavors, the flavors produced by carbonyl-amine reactions are usually positive in many foods and include, for example, the formation of Strecker aldehydes (Hidalgo & Zamora, 2004).

As discussed above, phenolic compounds take part in the described lipid oxidation pathways at different steps, providing a triple barrier against the lipid oxidation and its consequences. As shown in Fig. 6, the first barrier is the chelation of the transition

metals responsible for the initiation step. This would avoid the formation of the first radicals, which are essential for initiation of the process. Furthermore, the formation of phenol-metal chelates might have positive consequences because of the healthy properties described for these compounds, although some prooxidant effects have also been observed.

If free radicals are produced, phenolic compounds are also able to react with these radicals avoiding the propagation of the reaction. This free radical-scavenging ability would constitute the second defensive barrier of these compounds. As indicated in Fig. 6, phenols can react with many free radicals produced in the course of lipid oxidation pathway, producing in all cases the conversion of the lipid free radical into a lipid oxidation product and the breakage of the free radical chain.

Finally, phenolic compounds can also react with the carbonyl compounds produced in the lipid oxidation pathway, avoiding in that way the reaction of these carbonyl compounds with the surrounding amino compounds. This is the third protective barrier of phenolic compounds. This is a chemical reaction that produces in a first place the corresponding addition product that is later either stabilized to produce the corresponding carbonyl-phenol adduct or it can suffer a polymerization to produce brown lipid-phenol polymers. In addition, the formation of some carbonyl-phenol adducts might have positive consequences for the healthy properties of these compounds.

As observed in Fig. 6, several kinds of polymers can be produced during the lipid oxidation pathway when it takes place in the presence of amino compounds and phenols. In addition to the lipid-derived polymers, lipid-amine polymers, and lipid-

phenol polymers indicated in the figure, the formation of mixed lipid-amine-phenol polymers is also likely to be produced because of the presence carbonyl compounds in the firstly produced polymers might induce further reactions with both amino compounds and phenols.

7. Different parts in the flavonoid structure are responsible for the different protective functions

As discussed above, each protective effect has specific structural requirements, and these requirements are different for the different protective functions. This can be observed in Fig. 7, in which four flavones with different hydroxylation pattern are shown. When the carbonyl group is available, the metal ion complexes are preferentially formed between the keto group in the C-4 and the hydroxyl group in C-5. An ellipse between these two groups in the figure indicates the part of the molecule mainly responsible for its chelating activity. This activity should be present in the four selected flavones because the keto group in the C-4 and the hydroxyl group in C-5 are present in all of them.

The free-radical scavenging activity of flavonoids depends on the presence of catechol or *o*-trihydroxyl (pyrogallol) systems, because if these systems are not present, the flavonoids form relatively unstable radicals and are weak scavengers (Pannala, Chan, O'Brien, & Rice-Evans, 2001). For that reason, when Cai, Sun, Xing, Luo, and Corke (2006) studied the free-radical scavenging activity of the four flavones collected in Fig. 7, only luteolin and baicalein exhibited activity. These two compounds are the only compounds among those included in the figure that have catechol or *o*-trihydroxyl (pyrogallol) systems. The active free radical-scavenging system has also been marked in Fig. 7.

Finally, the carbonyl-scavenging activity needs the presence of phenolic carbons with a high electronic density. It occurs in luteolin, apigenin, chrysin and, to a lower extent, also in baicalein. The active carbonyl-scavenging region has been marked in Fig. 7.

All regions marked in Fig. 7 correspond to the most active regions for that protective effect. However, other regions can also play a role under determined circumstances. For example, a highly reactive carbonyl compound will react with a less reactive CH group if these groups are available and the most reactive are not.

As observed in Fig. 7, not all phenolics have all the protective functions. Furthermore, depending on the distribution of functional groups, some of them will be more efficient than others for the function(s) they have. Therefore, there will be, at least, seven groups of phenolics as a function of its activity: chelating agents, free radical scavengers, carbonyl scavengers, chelating and free radical scavengers, chelating and carbonyl scavengers, free radical and carbonyl scavengers, and chelating and free radical and carbonyl scavengers. A distribution of phenolic compounds among these groups remains to be carried out. However, the rules for structure-activity discussed above can provide a first approach for the expected activities of a specific compound.

8. Consequences of the different protective functions of phenolic compounds

Phenolics are frequently considered as a heterogeneous group of compounds having a protective function because of their antioxidative activity. However, the studies collected in this review show that both they do not have one function but three and they are not one group of compounds but several groups if the functions they can play are taken into account. Therefore, not all phenols are expected to be adequate to control a

455 determined process and, consequently, phenols should be selected as a function of the
456 kind of process that should be controlled. For example, PhIP formation in foods is a
457 serious concern because it produces colon, prostate, and mammary gland tumors in
458 rodent (Alaejos, Pino, & Afonso, 2008; Cheung, Loy, Li, Liu, & Yang, 2011;
459 Choudhary, Sood, Donnell, & Wang, 2012) and it is considered as possibly
460 carcinogenic to humans (IARC, 1993). As described above (Fig. 2), PhIP is a product of
461 carbonyl chemistry in foods. Therefore, PhIP formation will be inhibited by phenolic
462 compounds having a potent carbonyl scavenger function such as naringenin, as shown
463 experimentally (Cheng, Wong, Cho, Chu, Sze, H., Lo, Chen, & Wang, 2008). For that
464 reason, the use of carbonyl-scavenging phenols in marinating and meat processing
465 industries may be an attractive way to add value to meat products by minimizing the
466 risk of exposure to PhIP and improving nutritional characteristics of foods in which
467 antioxidants may be used in their formulation (Cheng, Wu, Zheng, Peng, Simon, Chen,
468 & Wang, 2007; Gibis & Weiss, 2012; Salazar, Arambula-Villa, Hidalgo, & Zamora,
469 2014). Nevertheless, this conclusion is only valid for PhIP because it is produced as a
470 consequence of carbonyl chemistry. If free radicals are involved, the use of phenols
471 with free radical scavenging activities should be required.

472 The different mechanisms involved in the protective action of phenolic compounds
473 are also likely related to the difficulty of determining the antioxidative activities of these
474 compounds. Phenolic activities are usually measured by several methods that usually
475 produce results that are not always coincident. This might be a consequence of the
476 different protective effects that are present simultaneously in the phenolic compound
477 and that can have either overlapping or opposing effects depending on the assayed
478 method. For example, if lipid oxidation products are determined, a phenol with only

carbonyl-scavenging abilities will suppress lipid oxidation products but it will not avoid the formation of free radicals.

A practical example of the different functions of phenolic compounds and the consequences on their properties can be observed in the differences between green and black tea (Gramza & Korczak, 2005). Green tea leaves are rich in catechins (its structure is shown in Fig. 1), which are expected to be good free radical and carbonyl scavengers. During fermentation for production of black tea, catechins are oxidized and converted into theaflavins, among other polymeric phenols (Vermeer, Mulder, & Molhuizen, 2008). Theaflavin (structure shown in Fig. 1) still has one *o*-diphenol system, but this system has been diluted in a bigger molecule. On the other hand, a carbonyl group has appeared and it still has two *m*-diphenol systems with a high carbonyl-scavenging potential. For that reason, teaflavin show metal chelating abilities but it is less free radical-scavenger than catechins (Gramza & Korczak, 2005). These changes might be related to the different health benefits of both kinds of tea. Thus, black tea consumption was inversely associated with Parkinson's disease risk, and green tea drinking was unrelated to Parkinson's disease risk (Tan, Koh, Yuan, Wang, Au, Tan, Tan, & Yu, 2008). On the contrary, a meta-analysis has shown that black tea does not have any protective role against coronary artery disease, but a tentative association of green tea consumption with a reduced risk of coronary artery disease was found (Wang, 2010). The reason of why a decrease in free radical scavenging activity and an increase in chelating and, perhaps, carbonyl-scavenging activities might affect differently to different diseases remains to be clarified, supposing that this change in phenol composition is one of the reasons for the different behavior of both kinds of tea.

9. Future research needs

Different to the free-radical scavenging ability of phenolic compounds, which has been objective of many studies, the role of carbonyl-scavenging ability of phenolic compounds for minimizing the consequences of either lipid oxidation or carbonyl chemistry in both foods and living beings has not been known until very recently. Therefore many questions still arise: how is the reactivity of the most toxic lipid oxidation products such as epoxyalkenals and oxoalkenals with phenolic compounds? Do only carbonyl compounds react with phenolic compounds or other lipid oxidation products such as epoxides are also able to react? Is there a relationship between the chain length of the lipid oxidation product and its reactivity with phenolic compounds? Is the structure of the lipid oxidation product important for determining which kind of phenolic compound will be the most appropriate for its elimination? How much amount of phenolic compounds will be needed to decrease the negative sensory impact of sensory-relevant lipid-derived reactive carbonyls?

After reaction with the lipid oxidation products, the free radical-scavenging part of the phenolic compound still remains intact: will the carbonyl-phenol adducts more or less free radical scavengers than the original phenols? Is it better to use two phenols with different activities (one being a free radical scavenger and the other being a carbonyl scavenger) or one phenol having the two functions? To this respect it has been shown the important role of the physical location of the phenolic compound on its efficacy against lipid oxidation (Iglesias, Pazos, Lois, & Medina, 2010).

The formation of carbonyl-phenol adducts imply the introduction of an aliphatic chain in the phenol which might convert these compounds into more lipophilic compounds: will these new compounds, at present considered emerging antioxidants

with an enormous potential (Liu, Jin, and Zhang, 2014), be produced naturally by the carbonyl-scavenging action of phenolic compounds?

Biological function of dietary phenolics is still poorly understood. Thus, for example, epidemiological studies inversely correlate colorectal cancer incidence with the intake of fruits and vegetables but not with their phenolic content. In addition, although preclinical studies using in vitro cell lines and animal models have reported anticancer effects of some phenolic compounds, these conclusions have been poorly translated into clinical trials (Núñez-Sánchez, González-Sarrias, Romo-Vaquero, García-Villalba, Selma, Tomás-Barberán, García-Conesa, & Espín, 2015). The studies presented in this review suggest that the phenolic compounds have different functions and their role might be better understood if they are classified according to their functions. Therefore, the use of groups of phenols with similar functions in the place of total phenolic content in epidemiological studies might produce better understandable results. Furthermore, the biological effects described so far for phenol-metal chelates and carbonyl-phenol adducts might also be playing a role in all these effects.

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778

779 **Figure legends**

780 **Fig. 1**. Chemical structures of catechin, quercetin, and theaflavin. Carbon numbering
781 and the letter usually employed to name the ring are indicated.

782 **Fig. 2**. PhIP formation from phenylacetaldehyde and creati(ni)ne.

783 **Fig. 3**. Alkanal addition to resorcinol and quercetin.

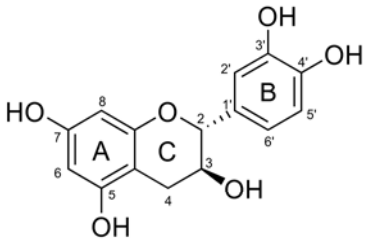
784 **Fig. 4**. Chemical structures of adducts formed between phenylacetaldehyde and either
785 naringenin or norartocarpetin.

786 **Fig. 5**. Reaction of 2-alkenals with resorcinol.

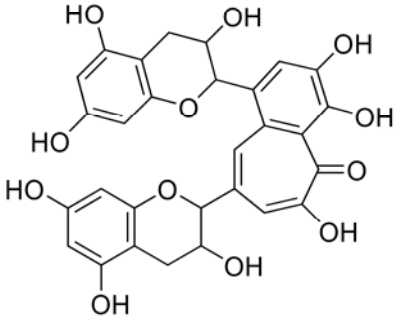
787 **Fig. 6**. The triple defensive barrier of phenolic compounds against the lipid oxidation
788 damage in food products. LH, lipid; L$^{\bullet}$, lipid radical; LO$^{\bullet}$, lipid alkoxyl radical;
789 LOO$^{\bullet}$, lipid peroxyl radical; LOOH, lipid hydroperoxide; $^{\bullet}$OH, hydroxyl radical.

790 **Fig. 7**. Presence of chelating, free radical-scavenging, and carbonyl-scavenging regions
791 in selected flavonoids.

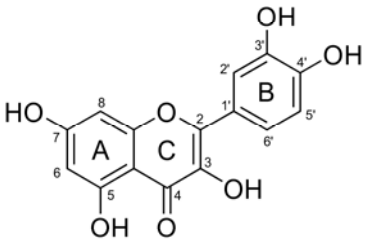
792



catechin



theaflavin

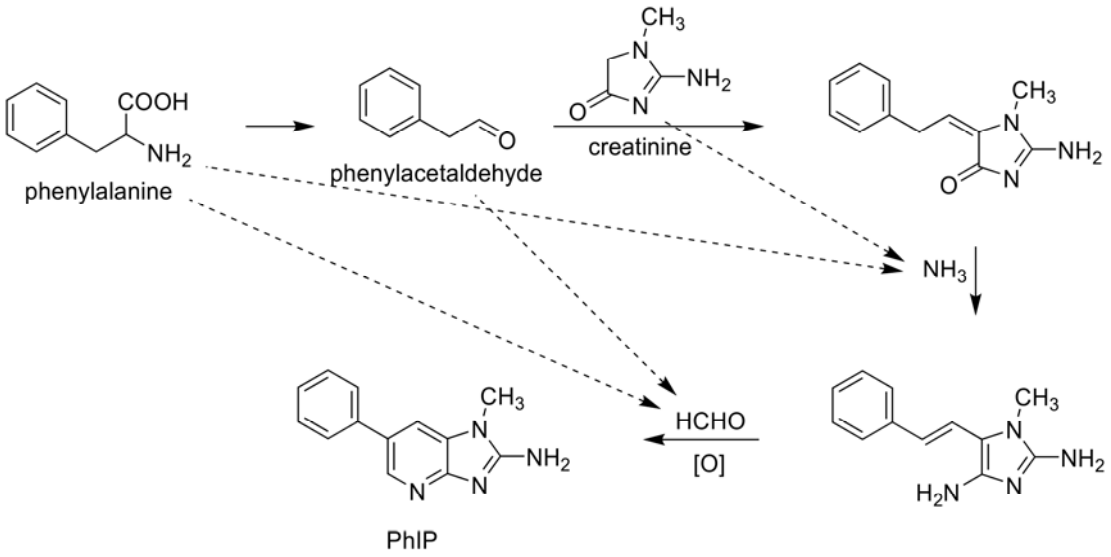


quercetin

793

794

795 **Figure 1**



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798 **Figure 2**

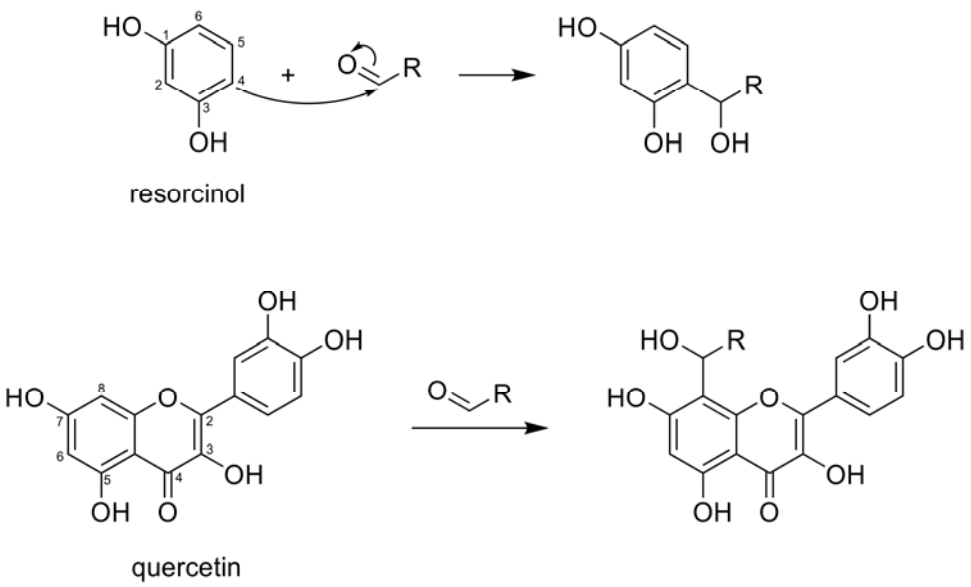
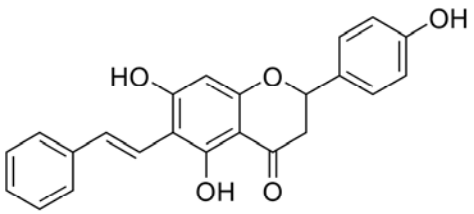
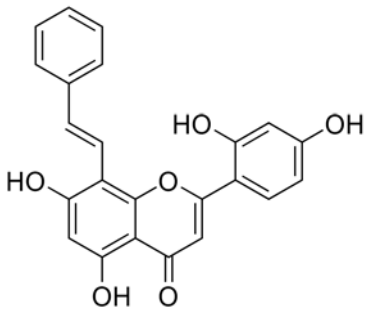


Figure 3



(*E*)-5,7-dihydroxy-2-(4-hydroxyphenyl)-6-styrylchroman-4-one



(*E*)-2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-8-styryl-4*H*-chromen-4-one

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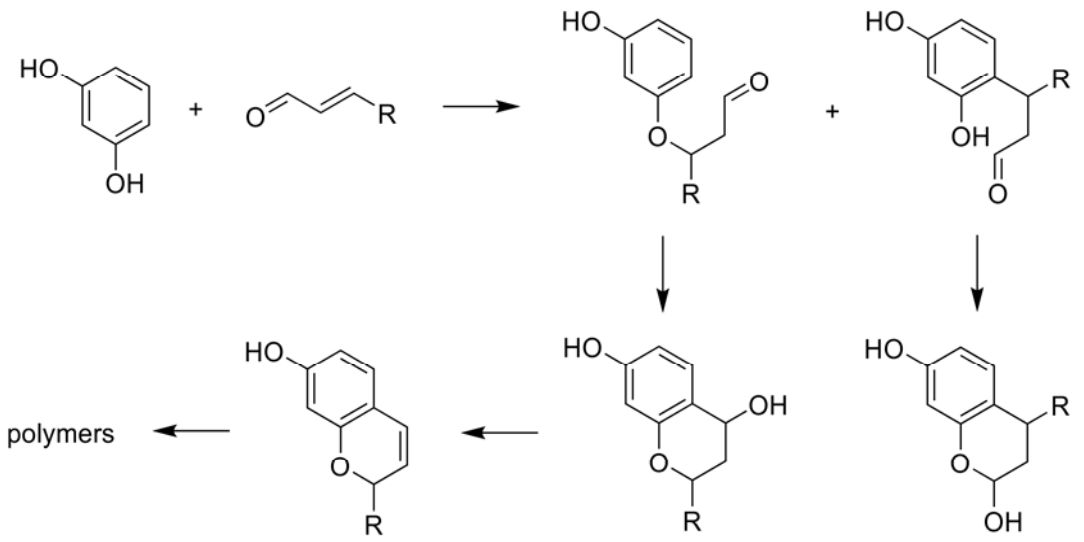
804 **Figure 4**



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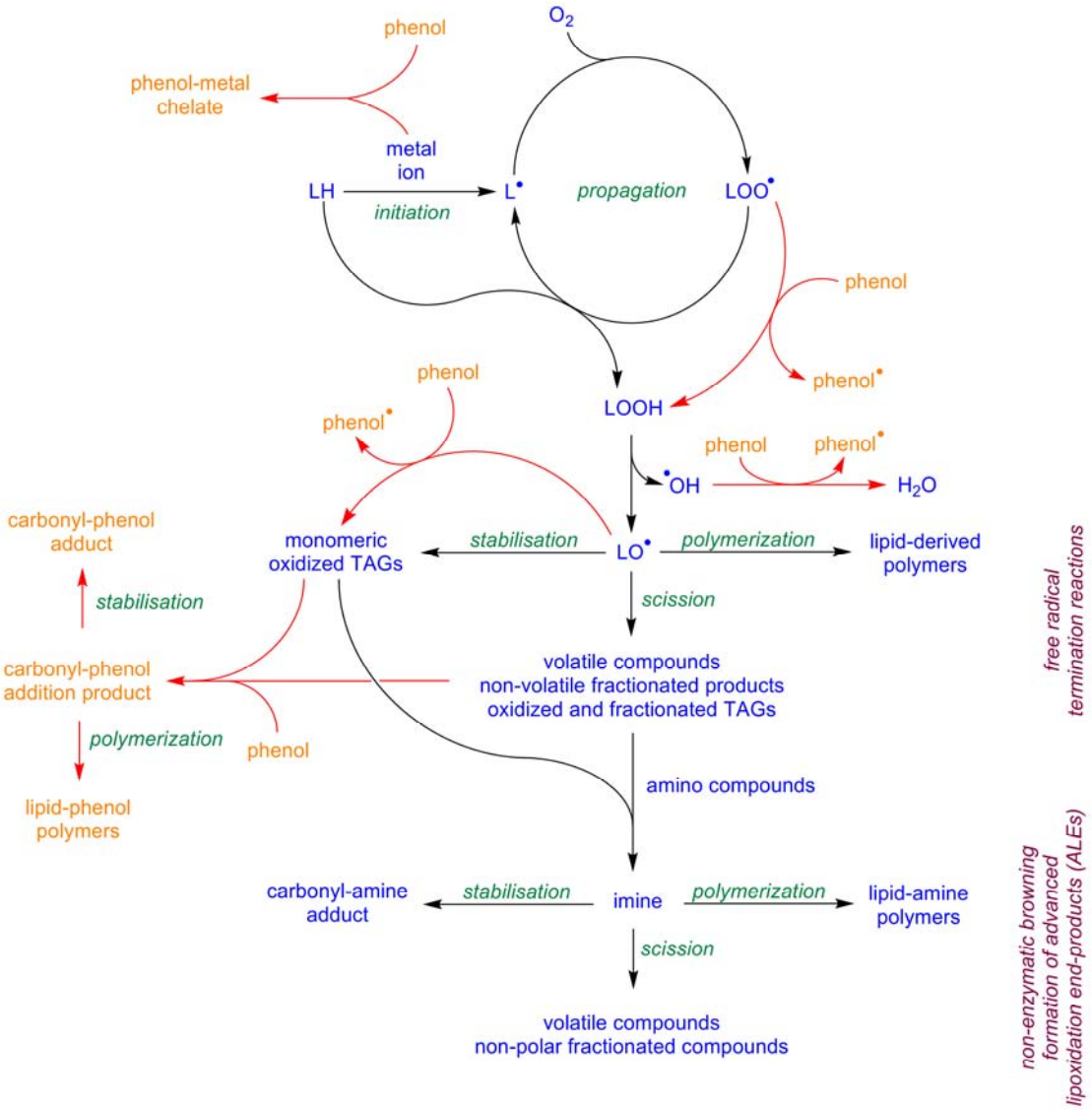
807 **Figure 5**



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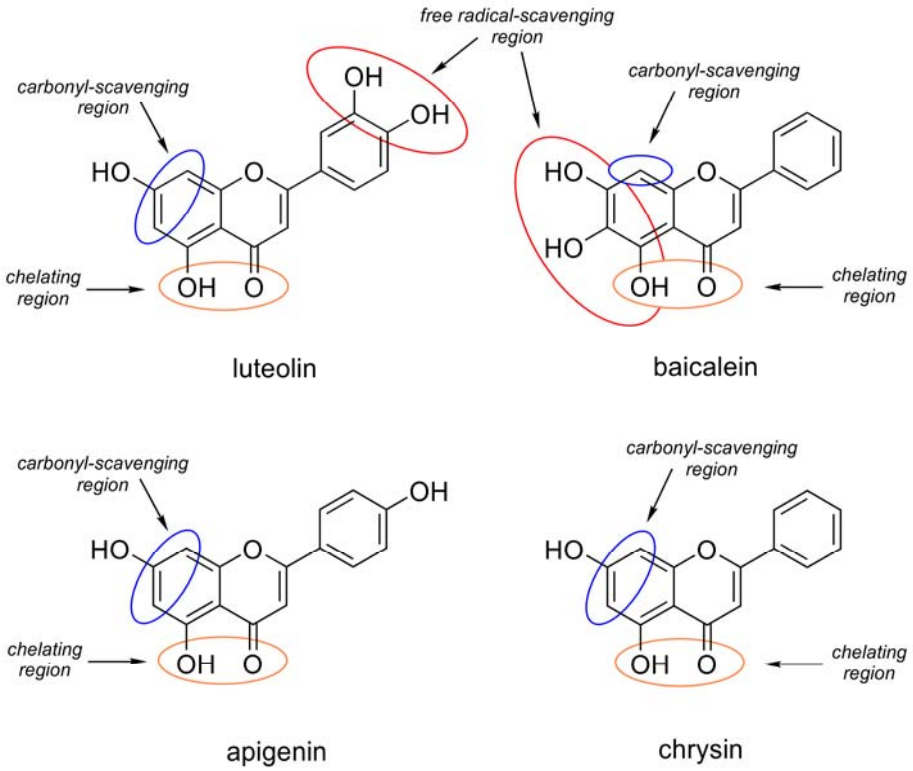
810 **Figure 6**



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813 **Figure 7**