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Review

What is responsible for antioxidant properties of polyphenolic compounds from plants?

Małgorzata Olszowy

Faculty of Chemistry, Maria Curie Sklodowska University, 20-031, Lublin, Pl. Marii Curie Sklodowskiej 3, Poland

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ABSTRACT

Due to the negative impact of reactive species (including free radicals) on humans and animals, the investigations to find effective substances (antioxidants), which protect living organisms against their damaging influence are carried out throughout the world. As most widespread synthetic antioxidants are suspected of having a noxious effect on the human body, more and more attention is paid to natural antioxidant compounds found in plants (especially phenolic compounds). The aim of this paper is to present the data about antioxidant activity of polyphenolic compounds with the emphasis on the main factors having influence on their antioxidant activity: chemical structure, ability to form hydrogen bonds, capability of metal ions chelation and reduction, adduct formation, kinetic solvents effect, mechanism of antioxidant reaction, capability of antioxidant enzyme activation and reduction potential.

1. Introduction

Intensive research on the metabolic role of oxygen has been carried out for the last 40 years. In particular, the oxidative stress-related diseases/disorders (neurodegenerative, cardiovascular, mitochondrial diseases and even cancer) have gained a special attention (Chaturvedi and Beal, 2013; Pham-Huy et al., 2008; Singh et al., 2004). As reported in the literature (Dreher and Junod, 1996; Pham-Huy et al., 2008; Son, 2012) reactive oxygen and nitrogen species (including free radicals) take part in their pathogenesis. In the living organism should there exist the balance between production and accumulation of these reactive species in cells and tissues as well as the ability of a biological system to detoxify of these forms. The lack of this balance causes a phenomenon called oxidative stress (Pizzino et al., 2017). At higher concentration, the reactive species have a negative impact on humans, plants and animals. This fact caused increasing interest in the attempts to understand the mechanism of free radical action and find effective substances (antioxidants) which protect living organisms against their damaging influence (Lü et al., 2010; Shalaby and Shanab, 2013). This protective role can take the forms of: preventing before formation of the reactive species, scavenging the free radicals, formation of chelate complexes with prooxidant metals, singlet oxygen and photosensitizers quenching, enzyme deactivation or activation, removing and repairing damages caused by the reactive species (Polumbryk et al., 2013).

The antioxidants used in medicine and industry are divided into two groups: natural and synthetic ones. As most widespread synthetic antioxidants are suspected of having a noxious effect on the human body (Dawidowicz et al., 2015a; Lobo et al., 2010), more and more attention is paid to natural antioxidant compounds found in plants (Balasundram et al., 2006; Gupta and Sharma, 2006; Olszowy and Dawidowicz, 2016). Among them, the most popular are the polyphenolic compounds which contain one or more hydroxyl groups in their structure (Cheynier et al., 2013). These compounds can be structurally divided into two major classes: phenolic acids (essentially hydroxybenzoic and hydroxycinnamic acids) and flavonoids (Simić et al., 2007). The former usually contain one benzene ring whereas the basic flavonoid structure consists of 15 carbon atoms arranged in three rings (C6–C3–C6), labelled A, C, and B, respectively (see Fig. 1) (Wojdyło et al., 2007). It is worth mentioning that polyphenols in plants are used not only for antioxidant defense but also for growth regulation, hormonal activity, antimicrobial activity, pH regulation, metabolism and induction of dormant period (Eghbaliferiz and Iranshahi, 2016; Inácio et al., 2013).

The aim of this paper is to present and discuss the antioxidant activity of polyphenolic compounds with the emphasis on the main factors having influence on their antioxidant activity including: chemical structure, ability to form hydrogen bonds, capability of metal ions chelation and reduction, adduct formation, kinetic solvents effect, mechanism of antioxidant reaction, capability of antioxidant enzyme activation and reduction potential.

E-mail address: malgorzata.olszowy@poczta.umcs.lublin.pl.

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Abbreviations

ABTS	2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt
AF	Adduct Formation
ArOH	Antioxidant
$ArOH^{\bullet+}$	Antioxidant Cation Radical
ArO	Aroxyl Anion
$ArO^{\bullet}$	Aroxyl Radical
BDE	Bond Dissociation Energy
DPPH	2,2′- diphenyl picrylhydrazyl
ETE	Electron Transfer Energy
ET-PT	Electron Transfer-Proton Transfer
IP	Ionization Potential
Nrf2	The nuclear factor erythroid 2–related factor 2
PA	Proton Affinity
PCET	Proton-Coupled Electron Transfer
PDE	Proton Dissociation Enthalpy
R^-	Radical Anion
$R^{\bullet}$	Radical
SPLET	Sequential Proton Loss Electron Transfer
TEAC	Trolox Equivalent Antioxidant Capacity
QH	Quercetin Anion
QC	Quantum Chemical

2. Mechanism of reaction

The antioxidant activity of polyphenolic compounds is associated with the capability of inactivation of reactive radical species. Neutralization occurs when antioxidant transfers its electron and/or hydrogen atom to the radical. As follows from the literature (Dawidowicz and Olszowy, 2012; Marković et al., 2013) scavenging of free radicals by phenolic compounds can follow four chemical pathways: Proton Coupled-Electron Transfer (PC-ET/HAT), Electron Transfer-Proton Transfer (ET-PT), Sequential Proton Loss Electron Transfer (SPLET) and Adduct Formation (AF, as discussed above). The balance between these mechanisms depends on the reaction environment.

The PC-ET/HAT mechanism proceeds by rapid donation of hydrogen atom to the radical species $R^{\bullet}$. The reaction in this mechanism is as follows:

$$ArOH + R^{\bullet} \rightarrow ArO^{\bullet} + RH$$

The SPLET mechanism takes place when at first the dissociation of antioxidant occurs and then the aroxyl anion (ArO^-) is formed. In the latter step the electron from the antioxidant anion can be transferred to the scavenged radical resulting in formation of the radical anion (R^-) which is protonated in the final stage of the reaction:

$$ArOH \rightarrow ArO^- + H^+$$

$$ArO^- + R^{\bullet} \rightarrow ArO^{\bullet} + R^-$$

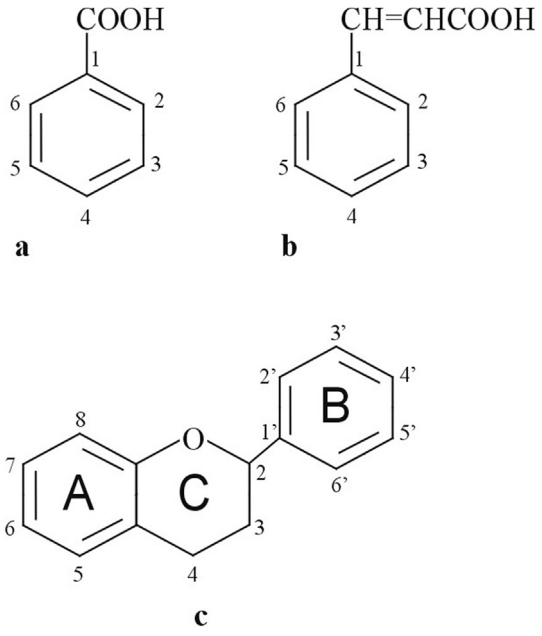

Fig. 1. Basic structures of: benzoic acid (a), cinnamic acid (b) and flavonoid (c).

$$R^- + H^+ \rightarrow RH$$

In the ET-PT mechanism the electron is transferred from the antioxidant to the scavenged radical. The formed antioxidant cation radical ($ArOH^{\bullet+}$) undergoes deprotonation and the hydrogen cation is transferred to the radical anion (R^-):

$$ArOH + R^{\bullet} \rightarrow ArOH^{\bullet+} + R^-$$

$$ArOH^{\bullet+} + R^- \rightarrow ArO^{\bullet} + RH$$

In the above mentioned mechanisms the final effect is the same but it is reached in a different way. Various antioxidant characteristics influence the mechanism: bond dissociation enthalphy (BDE) (particularly important in the HAT/PCET mechanism), proton affinity (PA) with the electron transfer energy (ETE) of ArO^- (important in the SPLET mechanism) and ionization potential (IP) of ArOH as well as proton dissociation enthalpy (PDE) of $ArOH^{\bullet+}$ in the ET-PT mechanism. The balance between these mechanisms depends on the reaction environment. The reaction between the phenolic antioxidants and radical occurs mainly by combination of the PC-ET and SPLET mechanisms. The former is slower and dominates in non-polar solvents of low dielectric constant and low basicity, whereas the latter is faster and is characteristic of solvents of high dielectric constant and high basicity supporting antioxidant ionization (Friaa and Brault, 2006). The ionization degree of phenolic antioxidant (ArOH) depends on both a bulk property of the solvent (its relative permittivity), and a molecular property (its relative ability to solvate, and hence stabilize anions (ArO^-)).

Finottii and Majo (Finotti and Majo, 2003) noticed that the *ortho*- and *para*-substituents of the formed polyphenolic radicals (i.e., after electron transfer or/and hydrogen transfer) are more stable than the *meta*-radical. Additionally, the ionizing solvent favours formation of non-covalent μ-stacked complexes between a large quercetin anion (QH^-) and other flavonoid anions with the DPPH radical (Foti et al., 2011). The formed adduct allows better electron transfer between the flavonoid anions and DPPH radicals as well as facilitates the radical neutralization.

Antioxidant activity of phenolic compounds (including flavonoids) is often predicted by determination of thermodynamic properties of the parent compounds (mentioned above) or of the antioxidant radical formed in the reaction, radical cations and anions. In the literature a lot of attention is paid to the estimation of the above mentioned parameters for determination of antioxidant reaction mechanism and the most reactive site in the structural compounds responsible for reactivity and participation in the preferred mechanism.

According to Marković et al. (2013), who performed the experiment with quercetin, among its five hydroxyl groups, the 4′- OH (ring B) exhibits the greatest ability to hydrogen atom donation. Of all OH groups in quercetin this group has the lowest BDE. The bond dissociation energies for the other groups change as follows: 3 - OH (ring C), 3′-OH (ring B), 7 - OH and 5 - OH (ring A). As mentioned above the

mechanism of antioxidant reaction can be determined by the reaction environment. The same authors found that in the aqueous medium the SPLET mechanism is favoured. This suggestion can be confirmed in terms of proton affinity and electron transfer energy. The lowest values of the mentioned parameter can be established for the 4′- OH (ring B) and for 7-OH (ring A) groups. According to Musialik et al. (2009) in alcohols the reaction between 10 examined flavonoids with the radical (DPPH radical) is faster than in the nonpolar solvent. The fast kinetics is associated with the electron transfer from the flavonoid anion to the neutralized radical because in the aqueous or alcoholic or water/alcoholic medium the solvent capability of both ionization and solvation of the antioxidant anion formed in the first stage of the reaction is higher (Litwinienko and Ingold, 2007). In the case of polar solvents the SPLET mechanism is favoured. The insightful analysis of structure acidity and structure activity for the chosen flavonoids (including quercetin), made by the authors indicates that the hydroxyl groups at position 7-OH (in the A ring) is the most acidic side in the molecule. According to the above mentioned authors deprotonation is the easiest in this group. The presence of the OH group at position 5 is responsible for the change of acidity of the 7-OH group.

3. Chemical structure

The antioxidant is a substance which exhibits ability to transfer electron and/or hydrogen atom during free radical neutralization (Brewer, 2011; Ndhlala et al., 2010; Pinelo et al., 2004). As commonly known, the antioxidant capability of phenolic compounds is dependent on the number of hydroxyl groups in the ring structure and their arrangements. An *ortho* position of hydroxyl groups confers high stability to the radical formed after radical neutralization process (Cuvelier et al., 1992). The higher the numbers of hydroxyl groups, the better their antioxidant properties (Villaño et al., 2005).

The data presented in the literature (Cuvelier et al., 1992; Rice-Evans et al., 1996) suggests that the antioxidant activity of phenolic acids can be associated with the hydroxyl groups which play a major role in antioxidant activity of phenolic compounds. Indeed caffeic acid (3,4-dihydroxy-cinnamic acid) with two hydroxyl groups exhibits better antioxidant properties than p-coumaric acid (4-hydroxycinnamic acid) which has only one hydroxyl group bound to the aromatic ring. *Para* position enhances the antioxidant activity compared to *ortho* and *meta* ones. Additionally the antioxidant activity of phenolic compounds depend on the electron-withdrawing properties of the carboxylate group in benzoic acids which have a negative effect on the H-donating abilities of hydroxy benzoates. According to Rice-Evans et al. (1996) the CO_2H group exhibits lower electron withdrawing potential when not adjacent directly to the hydroxyl groups. Hence, 3,5-dihydroxybenzoic acid (resorcylic acid) exhibits better antioxidant properties than 2,5-dihydroxy benzoic acid. Incorporation of $–CH_2-$ between the phenyl ring and the carboxylic acid group (as in hydroxyphenyl acetic acids) reduces impact of the carboxylate group.

It has been also found (Cuvelier et al., 1992; Piazzon et al., 2012; Rice-Evans et al., 1996) that.

- antioxidant activity of monophenols increases when one or two methoxy groups are located in the *ortho* position relative the hydroxyl groups. For example, sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid) is a better antioxidant compared to ferulic acid (3-methoxy-4-hydroxycinnamic acid). On the other hand ferulic acid is more effective than p-coumaric acid (4-hydroxycinnamic acid) *etc;*
- in the case of phenolic acids, the presence of methoxy group is not equivalent to that of hydroxyl group. For example, ferulic acid (3-methoxy-4-hydroxycinnamic acid) and vanillic acid (4-hydroxy-3-methoxybenzoic acid) are less effective antioxidants than caffeic acid (3,4-dihydroxy-cinnamic acid) and protocatechuic acid (3,4-dihydroxybenzoic acid);
- cinnamic acids are better antioxidants compared to benzoic acid due to the presence in their structure of the –CH═CH–COOH group which enhances the antioxidant activity more than the –COOH group (caffeic acid has better antioxidant properties than protocatechuic acid; the same is found also for ferulic and vanillic acids). Due to the delocalization of the electron in the double bond the radical formed from the antioxidant during the free radical neutralization is stabilized;
- alkyl esterification does not affect antioxidant properties, e.g. very similar antioxidant activity is exhibited by propyl gallate and gallic acid (trihydroxybenzoic acid) but esterification by quinic acid results in the antioxidant activity decrease (chlorogenic acid is a worse antioxidant compared to caffeic acid).

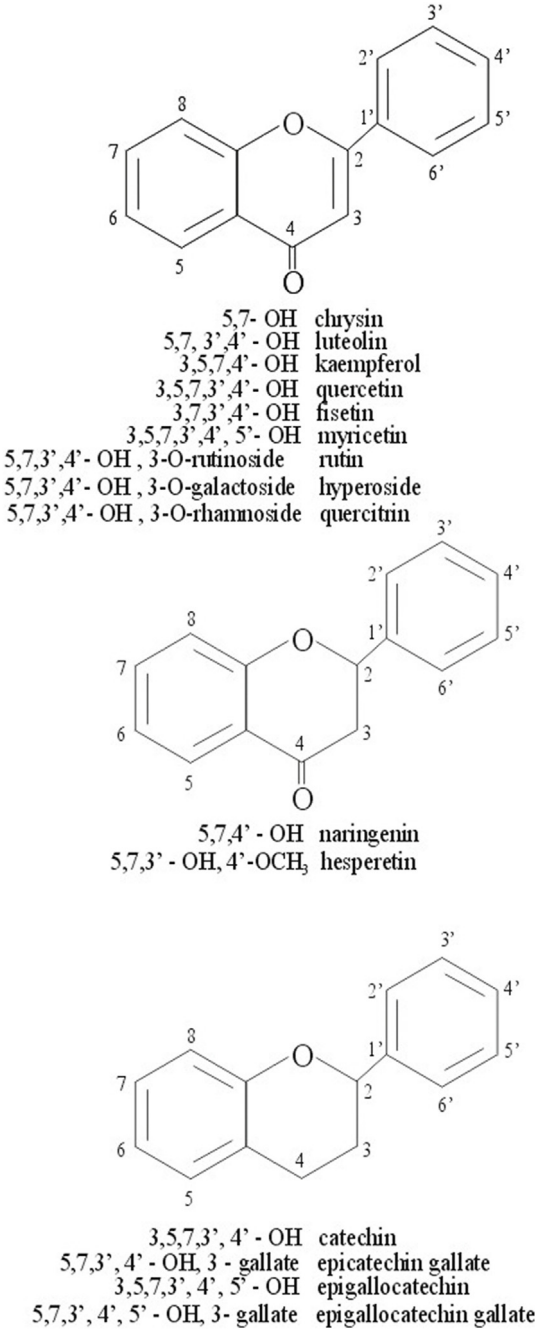

Fig. 2. Structures of flavonoids listed in the paper.

As for flavonoids (Freeman et al., 2010; Pietta, 2000; Vellosa et al., 2011) it was found that (for clarity see Fig. 2):

- the compounds with catechol moiety in the ring B, hindered phenols containing the methoxy group, and the monophenolic B ring exhibit different antioxidant properties. The catechol group in the B ring is characterized by better electron donating activity. The additional OH group in the B ring enhances the antioxidant activity (for example myricetin has better antioxidant properties than quercetin), the presence of only one OH group in the B ring reduces this activity (kaempherol is a worse antioxidant than quercetin). The presence of more than three hydroxyl groups in the aromatic ring (in the B ring of flavonoids) does not improve the compound antioxidant activity (Cuvelier et al., 1992);
- the presence of single hydroxyl group in 3′-position with a small electron-donating potential is responsible for low activity of compounds (hesperetin exhibits relatively low antioxidant activity). In contrast, the 4′-position would show more rapid formation of the phenoxyl radicals (Pannala et al., 2001);
- conjugation of the ring A with B by the heterocyclic, unsaturated ring C improves the antioxidant activity of polyphenolic compounds. Worse antioxidant properties are exhibited by flavonoids in which no conjugation between the rings B and C is present;
- a 2,3 double bond conjugated with the 4-oxo group favours electron delocalization;
- the presence of the 3-hydroxyl group in the heterocyclic ring also increases the antioxidant activity of phenolic compounds since the 3-OH group supports the reaction with free radicals (Butkovic et al., 2004). The worse antioxidant activity of flavones is due to the lack of the hydroxyl group. The reactivity of the 3-hydroxyl group is intensified by the electron donating effect of the hydroxyl groups at positions 5 and 7 (Rezk et al., 2002);
- conjugation between the 4′-hydroxyl group and the 3-hydroxyl group through the ring C enhances the antioxidant activity because the attraction of electron by the phenoxyl radical from the free radical is facilitated. The relatively high antioxidant activity of kaempferol, a flavonoid with the single hydroxyl group in the ring B, compared with the other monohydroxyl compounds can be explained using the above argument (Packer and Sies, 2001; Pannala et al., 2001);
- the additional hydroxyl or methoxyl groups at positions 5 and 7 of the ring A have less important influence on antioxidant activity of compounds compared to the hydroxyl groups in the ring B;
- generally glycosylation of 3-hydroxyl groups reduce the antioxidant properties of compounds. Hence rutin (quercetin-3-rutinoside) exhibits worse antioxidant activity than quercetin (Simić et al., 2007). However, according to Kähkönen and Heinonen (2003) glycosides in bulk oil are more effective than the aglycones;
- the presence of the pyrogallol group in the ring B (as for epigallcatechin) or galloylation of the 3-hydroxyl group (as for epigallcatechin gallate, epicatechin gallate) enhances the antioxidant activity (Braicu et al., 2011);
- in the case of isoflavones, the location of the ring B at position 3 of the heterocyclic ring increases their antioxidant properties (Pietta, 2000);
- the mixture of compounds, which do not have catechol groups or 2,3 double bonds can exhibit strong antioxidant properties. In the ORAC method the synergistic antioxidant effect was observed for the mixture of naringenin and hesperetin (Freeman et al., 2010).

4. Hydrogen bonding

The role of intramolecular hydrogen bonding on antioxidant activity of phenolic compounds has been discussed in the literature (Foti, 2007). Substituents in *ortho*-position (especially – methoxy, hydroxyl and amine groups are widespread in natural compounds) are considered as the H-bond acceptors. The presence of di-active groups (-OH) in the compound, –OH with $–NH_2$ and –OH with $–OCH_3$ is responsible for better antioxidant properties of compounds (Bendary et al., 2013; Hoelz et al., 2010). Due to these groups in the *ortho* position, compounds are capable of forming intramolecular hydrogen bonding which stabilizes the phenoxyl radical generated in the first step of the free radical neutralization. According to Leopoldini et al. (2004) hydrogen bond interactions are essential for enhancing the stability of antioxidant radical, so the catechol (*ortho* diphenolic) functionality is the main feature that affects the antioxidant activity. The formation of radical from hydroxyl group in catechol gives rise to species in which the electron appears to be delocalized over the whole molecule and stabilized by hydrogen bond interactions. A worse antioxidant activity of kaempferol results from the absence of the *ortho* diphenolic structure in the ring B. For this substituent BDE values are very small as compared to phenol. Participation of these groups in antioxidant radical formation gives rise to species in which the odd electron appears to be delocalized over the whole molecule and stabilized by hydrogen bond interactions. Intramolecular interactions, which influence on the antioxidant activity of polyphenols should be taken into account in order to correctly predict the antioxidant behaviour of the more complicated natural polyphenols (Ali et al., 2013; Amorati et al., 2003).

5. Metal ions chelation and reduction

As follows from the literature (Shahidi and Zhong, 2015), the antioxidant activity of polyphenols, consists in not only the ability to neutralize a free radical but also to inhibit the oxidation process. This noxious process is responsible for deterioration of food products and living organisms aging. The oxidation process proceeds faster in the presence of ionic metals such as copper and iron. Metals catalyze food radical formation by abstracting hydrogen (Choe and Min, 2009). They also promote the decomposition of hydroperoxides or take part in the production of hydroxyl radical in the Fenton reaction (Craft et al., 2012). The antioxidant activity of polyphenolic compounds connected with inhibition of the oxidation process can result from their ability to chelate and/or to reduce metal ions. As reported in the literature (Gülçin, 2006) the compounds with two or more groups such as: OH, –SH, –COOH, $–PO_3H_2$, C═O, $–NR_2$, –S– and –O– are able to chelate metal ions. The ortho position of these groups increases chelation ability (Santos et al., 2017). Due to the presence of –OH groups in their structure, e.g. caffeic acid (Adjamani and Asare, 2015), gallic acid, chlorogenic acid (Andjelkovic et al., 2006), protocatechuic acid (Yoshino and Murakami, 1998), the polyphenolic compounds are good metal ion chelators.

As follows from the studies flavonoids are capable of chelation iron and copper ions which is related to their structure and pH (Mira et al., 2002). According to Fernandez et al. (2002) and Symonowicz and Kolanek (2012) three potential coordination sites in the polyphenolic compounds (flavonoids) are between:

- 5-OH (ring A) and 4-carbonyl group (ring C)
- 3-OH and 4-carbonyl group (both in ring C)
- 3′-OH and 4′-OH group in ring B

The above statement was made by Mira et al. (2002) who proved that at pH 7.4 and 5.5 the polyphenolic compounds (flavonoids) exhibit ability to chelate Cu^{2+} in the same site probably between the 5-OH and 4-carbonyl groups, while at pH 7.4 myricetin and quercetin appear to chelate additional Cu^{2+} in the *ortho*-catechol group. They also stated that in the case of myricetin and quercetin Fe^{3+} chelation is possible after reduction of Fe^{3+} to Fe^{2+} prior to binding of metal ion. The Fe^{3+} reduction ability is connected with the presence in the compound structure:

- 2, 3-double bond in the ring C
- 3-OH and 4′-OH group in the ring B
- 3-OH in the ring C

The copper reducing capability can depend largely on the number of hydroxyl groups (Mira et al., 2002). For nonflavonoid polyphenolic compounds formation of an inactive Fe^{2+} polyphenolic complex by reducing Fe^{3+} was observed by Yoshino and Murakami (1998).

6. Adducts and dimers about antioxidant properties

As mentioned above, the number of hydroxyl groups and other aromatic ring substituents are two main factors associated with the antioxidant activity of phenolic compounds (Bendary et al., 2013). Arts et al. (2003) determined the antioxidant activity of catechol, resorcinol and hydroquinone (see Fig. 3) using the ABTS method (employing 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt). All compounds possess two hydroxyl groups in the *ortho*, *meta* and *para* positions, respectively. According to the Hammett sigma (σ)values (substituent parameter σ is derived from the acidity constants, Ka's of substituted benzoic acid) of aromatic hydroxyl groups, in particular those in position 3, exhibit strong capability of electron withdrawal from other compounds or radicals (σ = 0,12) whereas the hydroxyl groups located in 2,4 position have an electron donating effect (σ = -0,37). On this basis, resorcinol should possess weaker antioxidant properties because the reaction of resorcinol with a radical would be reduced by the electron-withdrawing effect of the –OH group in the *meta*-position. The presented results are surprising because the obtained value of Trolox Equivalent Antioxidant Capacity (TEAC) for resorcinol is ca. twice as high as those established for catechol and hydroquinone. The accurate reaction between the resorcinol and ABTS cation radical points out that the better antioxidant activity of resorcinol results from formation of a new product (adduct) which also shows antioxidant activity. Hence the more intense antioxidant activity of resorcinol does not reflect the antioxidant activity of resorcinol itself, but is the sum of antioxidant activities which have a parent compound (resorcinol) and a product of its reaction with the ABTS cation radical (Arts et al., 2003). The formation of covalent adduct between the phenolic compounds and ABTS cation radical was also observed for the other phenolic compounds, for example arbutin − glucoside of hydroquinone which is present in bearberry, bilberry, strawberry tree, or in pear (Tai et al., 2016), phlorglucinol and catechin (Osman et al., 2006), propofol, chrysin (Arts et al., 2004)), rutin, hyperoside, quercitrin, quercetin (Liu et al., 2014) and other monohydroxyl compounds (Pannala et al., 2001). The formed adducts were mainly combination of the phenolic compounds with the fragment from the ABTS cation radical (as confirmed by the band in the UV spectrum at ca. 226 and 344 nm). In many cases the new compounds exhibit antioxidant properties which make prediction of actual antioxidant properties impossible in terms of chemical structure of a parent compound. The formation of adduct with the oxidized form of the polyphenol and dimer was also observed using the DPPH method (Osman, 2011). Then in the case of catechol, hydroquinone and resorcinol there was no adduct formation and the antioxidant activity of these compounds determined by means of the DPPH method decreases as follows catechol > hydroquinone > resorcinol (Bendary et al., 2013). It is different from the results obtained by Arts et al. (2004) in the ABTS assay. The formation of polymeric oxidation product of properties similar to that of the parent compound antioxidant activity was observed during the studies of antioxidant activity of polyphenolic compounds in micelles (Roginsky, 2003) or their oxidation in the flow column electrolysis (Hotta et al., 2001). The dimer formation was observed by Pannala et al. (2001) during the ABTS radical cation neutralization by monohydroxyl compound and hindered phenol. They also found that the ferulic acid dimer exhibits antioxidant properties which are better than those of the monomer.

7. Kinetic solvent effect

It has been noted that the solvent influences the kinetics of the reaction between radical and antioxidant (Foti and Ruberto, 2001; Thavasi et al., 2009; Tsimogiannis and Oreopoulou, 2004). The solvent takes part in the reaction between the radical and antioxidant. It participates in the electron or/and hydrogen transfer from the antioxidant to the neutralized radical. The solvents are characterized by different ability to donate or accept protons in the hydrogen bond (H–B). When the ability to accept protons increases, the reaction rate constant decreases. The antioxidant groups which are capable of giving protons to the radical are blocked by a solvent and in this way they are deactivated. Hydrogen atom transfer from the antioxidant to radical is impossible for the steric reason (Amorati et al., 2017). This so-called "kinetic solvent effect" depends only on properties of solvent but is independent of radical which is neutralized (Litwinienko and Ingold, 2007). The action of polyphenolic antioxidant is associated with the mutual equilibrium between the "free" and "blocked" groups in the antioxidant structure (Banks et al., 1996; Foti and Ruberto, 2001). Two parameters can impact on the kinetic solvent effect. The literature describes the ability of solvent to act as hydrogen-bond acceptors (labelled β) and of phenolic antioxidant to act as hydrogen-bond donors (labelled α) (Dawidowicz et al., 2015b; Litwinienko and Ingold, 2004). "Abnormal solvent effect" can be discovered in the reaction between the phenolic compounds and the radical (DPPH radical) in alcohols (Litwinienko and Ingold, 2007). The mechanism SPLET, in which a solvent facilitates the antioxidant dissociation and stabilization of the formed antioxidant ions, was explained in terms of abnormal solvent effect.

Additionally, the impact of solvent on the antioxidant activity is connected with the solvent capability of association. Forming different multiplex clusters facilitates or disturbs the electron and/or hydrogen transfer in the measuring system (Dawidowicz et al., 2012, 2015b; Dawidowicz and Olszowy, 2013).

8. Reduction potential

The antioxidant activity of phenolic compounds is also connected with the reduction potential. Butkovic et al. (2004) during the experiments observed the linear correlation between the reduction potentials of flavonoids and the logarithm of the rate constants for the reaction with the DPPH radicals. The lower reduction potential, the more likely the molecule is to donate its electron to the radical. The values of reduction potentials for the chosen phenolic antioxidant are listed in Table 1.

Compounds with low oxidation potentials (Ep_a < 0.45 V) show the antioxidant activity, whereas those with the high Ep_a values (> 0.45 V) act also as prooxidants (Simić et al., 2007). For example, the prooxidant activity can be observed for hesperidin and naringenin (Ep_a values > 0.45 V) which are able to induce oxidized alterations in the liver cells (Constantin et al., 2013). Additionally, a structural analysis of the phenolic compounds confirmed that the multiple OH substitution and conjugation of compounds have impact on their electrochemical profile. The presence of a second hydroxyl group in the benzene ring result in considerable reduction of Ep_a values (see kaempherol and quercetin in Table 1). It was observed that oxidation of phenolic compounds with

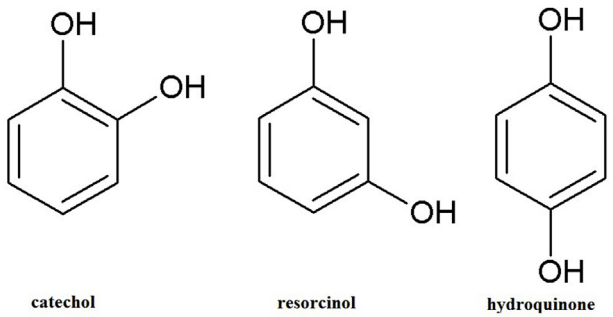

Fig. 3. Chemical structures of catechol, resorcinol and hydroquinone.

Table 1
Values of reduction potential for chosen phenolic compounds.

Compounds	Ep_a [V][a]
caffeic acid	0.31 (Sousa et al., 2004)
(+) catechin	0.36 (Butkovic et al., 2004)
chlorogenic acid	0.39 (Sousa et al., 2004)
ferulic acid	0.53 (Sousa et al., 2004)
fisetin	0.39 (Gil and Couto, 2013)
hesperetin	0.72 (Freeman et al., 2010)
kaempferol	0.39 (Butkovic et al.,2004)
luteolin	0.41 (Freeman et al., 2010)
myricetin	0.20 (Freeman et al., 2010)
naringenin	0.76 (Freeman et al., 2010)
p-coumaric acid	0.59 (Freeman et al., 2010)
quercetin	0.29 (Freeman et al., 2010)

[a] First voltammetry peak.

the hydroxy group in the *ortho* position leads to the formation of quinone and to lowering of the electrochemical potential (Sousa et al., 2004; Trabelsi et al., 2004). Simić et al. (2007) noted that introduction of a methoxy group instead of a hydroxyl one in the position *meta* relation to COOH shifts the Ep_a toward a more positive value (see ferulic and caffeic acids in Table 1). The electrochemical oxidation process of polyphenolic compounds (especially flavonoids), has not been fully examined so far. For the polyphenolic compounds on voltammograms a few peaks are observed. As follows from the literature (Brett and Ghica, 2003; Macikova et al.,. 2012) the first voltammetric peak, which occurs at low reduction potential, corresponds to two-electron oxidation of –OH groups at positions 3′ and 4' in the B ring. The presence of the other peaks (the second and third *etc.*) is associated with the oxidation of the C-3 hydroxyl group (also a very small anodic peak because the hydroxyl group can form the intermolecular hydrogen bond with the oxygen at position 4 in the ring C) and with the presence resorcinol moiety in the A ring (position 5 and 7) occurring at a high reduction potential. This statement was confirmed during the examination of compounds in which structure lacks the C-3 hydroxyl group due to glycosylation (for example for rutin only two anodic peaks – one from the catechol moiety at 0.4 V in the ring B and the other one at ca. 1 V from the resorcinol moiety in the A ring are observed) (De Oliveira-Roberth et al., 2012; Zielińska et al., 2010).

9. Antioxidant enzymes activation

The protective effects of polyphenolic compounds in the biological systems are associated with not only their the activity of enzymes which are engaged in the oxidation process in living organisms (capability of electrons transfer to free radicals or chelation of metal, but also with activation of antioxidant enzymes (Butkovic et al., 2004). Some phenolic compounds (especially flavonoids) can influence the activity of enzymes which are engaged in the oxidation process in living organisms (Martín et al., 2010; Procházková et al., 2011). It is known from literature that flavonoids are able to activate of glutathione - related enzymes (glutathione S transferase, glutathione peroxidase and glutathione reductase) (Masella et al., 2004). Yeh and Yen (2006) noted that gentisic acid, gallic acid, ferulic acid and p-coumaric acid, which were dosed to rats (at a dosage of 100 mg/kg body weight for 14 consecutive days), caused the increase of activity of superoxide dismutase, glutathione peroxidase, and catalase in the liver and small intestine. Also better activity of antioxidant enzymes was noted by Silva et al. (2012) during the examination of the aqueous extract and its polyphenolic fractions of *Halimeda opuntia* (Linnaeus) Lamouroux which were investigated in rats with chemically induced liver injury. The obtained results can be explained by an increase of gene transcription (mRNA) as well as the Nrf2 transcription factor which are caused by phenolic compounds (including flavonoids). The higher expression of the Nrf2 is responsible for induction of the so-called phase II antioxidant enzymes which are very important in chemoprevention (Krysztofiak and Krajka-Kuźniak, 2015). As reported in the literature (Afsar et al., 2016; Bode and Dong, 2003; Han et al., 2007), the effects of polyphenolic compounds on the antioxidant enzyme expression and activity could be associated with modification of signal transduction pathways. This activity of polyphenolic compounds as well as ability to activate a number of cellular kinases (Bahadoran et al., 2013; Hasima and Ozpolat, 2014; Pandey and Rizvi, 2009) have positive impact on human health.

10. Theoretical aspects in determination of antioxidant properties of polyphenolic compounds

In parallel with the increasing experimental research concerning the antioxidant polyphenolic compounds the huge interest in theoretical chemistry applications in the estimation of their antioxidant activity is observed (Galano et al., 2016). The quantum chemical (QC) studies have provided a significant amount of data on reactions mechanisms between the phenolic compounds and free radicals (Alov et al., 2015; Marković et al., 2016; Perez-Gonzalez et al., 2012). Hence, many computational protocols have been developed to produce reliable quantitative data concerning the kinetics of radical-molecule reactions in solutions. The reported theoretical data show that different reaction mechanisms in various solvents, the largest contributions of the given mechanism in neutralization of different radicals, and reactivity of compounds in comparison with another antioxidant can be determined (Galano et al., 2012, 2015; León-Carmona et al., 2012; Leopoldini et al., 2011a,b; Mazzone et al., 2016). To estimate the antioxidant activity of phenolic compounds the OH groups acidity values and the binding energies for the complexation process have been very often studied employing theoretical and computational methods (Leopoldini et al., 2011a,b). In many papers the deprotonation mechanisms are investigated using computational chemistry within the density functional theory framework for many phenolic compounds (Álvarez-Diduk et al., 2013; Leopoldini et al., 2011a,b). The QC calculated parameters based on the electronic properties of the phenolic molecules and the phenoxyl radicals, radical cations or phenoxide anions (BDE, IP, PA, ETE) are very informative in the prediction of antioxidant activity of phenolic compounds (Filipović et al., 2015; Jeremić et al., 2017; Leopoldini et al., 2004). The theoretical chemistry has confirmed that both the dissociation energy of phenolic hydroxyl bond and the ionization potential are the main factors which determine the antioxidant activity of these compounds (Iuga et al., 2012; Leopoldini et al., 2010, 2011a,b; Milenković et al., 2017; Stepanić et al., 2013). Moreover, the calculated data are in good agreement with the experimental values, which support the reliability of the calculations presented in many papers (Alberto et al., 2013; Marino et al., 2014).

11. Some other factors affecting antioxidant activity of phenolic compounds

As it was shown in our previous papers the antioxidant activity of phenolic compounds depends also on the other components not exhibiting antioxidant properties which are present in the measuring system. Such factors as type of metal ions and their concentration, as well as pH influence on the estimation of antioxidant activity of compounds in the DPPH, ABTS and β-carotene bleaching assays (Dawidowicz and Olszowy, 2010, 2011, 2015).

The antioxidant activity of phenolic compounds estimated by the DPPH, ABTS and β-carotene bleaching assays decreases with metal ions concentrations. In the case of experimental methods which employ the colour radicals (DPPH and ABTS assays) in the acidic environment, the antioxidant activities are worse which is associated with low dissociation of the examined compounds and another mechanism of radical neutralization (Dawidowicz and Olszowy, 2012). In the β-carotene bleaching assay the higher hydrogen ions concentration causes an

apparent increase in the antioxidant activity of the phenolic compound which is due to inhibition of peroxyl radicals formation in the presence of hydrogen ions. Contrary to hydrogen ions, alcalic metal ions accelerate the formation of peroxyl radicals and in this way they are responsible for the acceleration of β-carotene depletion and worse antioxidant activity (Dawidowicz and Olszowy, 2010, 2015).

The presence of water in the measuring systems causes an increase of antioxidant activity of phenolic compounds as observed in the DPPH and ABTS assays (Dawidowicz and Olszowy, 2011; Dawidowicz et al., 2012). This fact can be explained in terms of the change of solvent structure in the presence of water (Dawidowicz et al., 2015b) - water takes part in breaking down of solvent clusters facilitating hydrogen and/or electron transfer during the radical neutralization.

Also in the case of the ABTS and DPPH methods, during measuring of antioxidant activity of polyphenolic compounds spectrophotometrically, the attention should be paid whether the spectrum of the antioxidant or real biological system does not coincide with the wavelength used to monitor colour radical neutralization (Olszowy and Dawidowicz, 2018).

12. Prooxidant activity of polyphenolic compounds

According to Yordi et al. (2012) polyphenols are considered “double edged swords” in the cells, besides the antioxidant properties they can exhibit also prooxidant activity. It is commonly known that many polyphenolic compounds for example: quercetin, myricetin, kaempherol, caffeic, chlorogenic and ferulic acids, catechin, epigallocatechin, epiallocatechin-3-gallate act as pro-oxidants (Chedea et al., 2010; Chobot and Hadacek, 2011; Lambert and Elias, 2010; Zheng et al., 2008; Zhou and Elias, 2013). Several studies have shown that under certain conditions, such as: high concentrations, high pH and the presence of redox-active transition metals, polyphenols can exhibit this activity. This is connected with the formation of labile aroxyl radicals, or labile redox complexes with metal cation. The former can react with oxygen causing the formation of $O_2^{-\bullet}$ and can also form ternary adducts between DNA, copper ions and flavonoids or complex combination of semiquinones and quinones.

As mentioned above, the prooxidant activity depends on pH. The reduced transition metals are characterized by better solubility and stability at an acidic pH which is responsible for the induction of prooxidative reactions (Eghbaliferiz and Iranshahi, 2016).

Also the chemical structure of polyphenols has influence on their prooxidant activity. Ortho-di/trihydroxylated compounds are more capable of prooxidant activity than their mono-hydroxylated as well as galloyl moieties (in the case of gallates) have impact on it (Cheng and Breen, 2000; Chobot and Hadacek, 2011; Touriño et al., 2008). Additionally, apart from the number of hydroxyl groups and their positions, the presence of a double bond in the ring C, steric hindrance, affinity for peroxidase and concentration are important factors for the prooxdiant activity of flavonoids (Eghbaliferiz and Iranshahi, 2016).

Most experimental research concerning activities of polyphenols has been carried out “in vitro”. In many papers the question about prooxidant action of polyphenols “in vivo” has appeared (Halliwell, 2008). To answer this question there should be considered the following factors: concentration of transition metals in the organism (concentration of these metals is often significantly lower than that used in the experiments. The exception is when the amounts of these metals increase in the plasma which can be associated with some diseases), concentration of polyphenols in the plasma (due to their very low bioavailability), antioxidant defence systems which are present in each cell (these systems include antioxidant enzymes and other antioxidant compounds) as well as the fact that polyphenols and other dietary antioxidants are consumed as mixtures (Eghbaliferiz and Iranshahi, 2016). Hence, the prooxidant activities of polyphenols need to be further examined, particularly in the systems which reflect the actual conditions in the human body. This is a very important issue because the prooxidant molecules can be used as selective cytotoxic agents against cancer cells as they are responsible for the increasing levels of reactive species in them. For this purpose some polyphenolic compounds (curcumin, epigallocatechin gallate, resveratrol) are proposed as anticancer agents (León-González et al., 2015).

13. Conclusions

The recent research carried out in the field of natural antioxidants developed the knowledge about natural and healthy compounds that are available from plants. Among them, phenolic compounds are very popular because they are natural, and have antioxidant activities that are equally good or even better than the synthetic antioxidants. This fact makes them particularly attractive for commercial food producers because of progressively higher consumer demand for natural and safe food ingredients.

It is considered that the antioxidant effectiveness of these aromatic antioxidants is proportional to the number of –OH groups present in the aromatic ring(s). Depending on the arrangement of the –OH groups, these compounds can also chelate prooxidative metals, activate antioxidative enzymes, form adducts of antioxidant properties. In additionally are also able to form intramolecular hydrogen bonds between the nearby functional groups in both phenol and phenoxyl radicals. Moreover, their antioxidant activities can depend on the reaction medium – solvent can affect the mechanism of reaction and availability of antioxidant groups (kinetic solvent effect). Also metal ions (type and their concentration) found in the measuring system, as well as pH can affect the antioxidant properties of phenolic compounds. Hence, to make predictions on the antioxidant behaviour of phenolic compounds all chosen factors should be taken under consideration.

Contributions

Olszowy Małgorzata performed the all manuscript (designed and wrote the manuscript)

Conflicts of interest

The author confirms that this article content has no conflict of interest.

References

Adjamani, J.P., Asare, P., 2015. Antioxidant and free radical scavenging activity of iron chelators. Toxicol. Rep. 2, 721–728.
Alberto, M.E., Russo, N., Grand, A., Galano, A., 2013. A physicochemical examination of the free radical scavenging activity of Trolox: mechanism, kinetics and influence of the environment. Phys. Chem. Chem. Phys. 15, 4642–4650.
Ali, H.M., Abo-Shady, A., Eldeen, H.A.S., Soror, H.A., Shousha, W.G., Abdel-Barry, O.A., Saleh, A.M., 2013. Structural features, kinetics and SAR study of radical scavenging and antioxidant activities of phenolic and anilinic compounds. Chem. Cent. J. 7, 53–62.
Alov, P., Tsakovska, I., Pajeva, I., 2015. Computational studies of free radical-scavenging properties of phenolic compounds. Curr. Top. Med. Chem. 15, 85–104.
Álvarez-Diduk, R., Ramírez-Silva, M.T., Galano, A., Merkoçl, A., 2013. Deprotonation mechanism and acidity constants in aqueous solution of flavonols: a combined experimental and theoretical study. J. Phys. Chem. B 117, 12347–12359.
Amorati, R., Lucarini, M., Mugnaini, V., Pedulli, G.F., 2003. Antioxidant activity of o-bisphenols: the role of intermolecular hydrogen bonding. J. Org. Chem. 68, 5198–5204.
Amorati, R., Baschieri, A., Cowden, A., Valgimigli, L., 2017. The antioxidant activity of quercetin in water solution. Biomimetics 2 (9), 1–13.
Andjelkovic, M., Camp, J.V., Meulenaer, B., Verhé, R., 2006. Iron-chelation properties of phenolic acids bearing catechol and galloyl groups. Food Chem. 98, 23–31.
Arts, M.J.T.J., Dallinga, J.S., Voss, H.P., Haenen, G.R.M.M., Bast, A., 2003. A critical appraisal of the use of the antioxidant capacity (TEAC) assay in defining optimal antioxidant structures. Food Chem. 80, 409–414.
Arts, M.J.T.J., Haenen, G.R.M.M., Voss, H.P., Bast, A., 2004. Antioxidant capacity of reaction products limits the applicability of the Trolox Equivalent Antioxidant Capacity (TEAC) assay. Food Chem. Toxicol. 42, 45–49.
Afsar, T., Trembley, J.H., Salomon, C.E., Razak, S., Khan, M.R., Ahmed, K., 2016. Growth inhibition and apoptosis in cancer cells induced by polyphenolic compounds of

Acacia hydaspica: involvement of multiple signal transduction pathways. Sci. Rep. 6, 1–12.
Bahadoran, Z., Mirmiran, P., Aziz, F., 2013. Dietary polyphenols as potential nutraceuticals in management of diabetes: a review. J. Diabetes Metab. Disord. 12, 1–9.
Balasundram, N., Sundram, K., Samman, S., 2006. Phenolic compounds in plants and agri-industrial by-products: antioxidant activity, occurrence, and potential uses. Food Chem. 99, 191–203.
Banks, J.T., Ingold, K.U., Lusztyk, J., 1996. Measurement of equilibrium constants for complex formation between phenol and hydrogen-bond acceptors by kinetic laser flash photolysis. J. Am. Chem. Soc. 118, 6790–6791.
Bendary, E., Francis, R.R., Ali, H.M.G., Sarwat, M.I., Hady, S.E., 2013. Antioxidant and structure-activity relationships (SARs) of some phenolic and anilines compounds. Ann. Agric. Sci. 58, 173–181.
Bode, A.M., Dong, Z., 2003. Signal transduction pathways: targets for green and black tea polyphenols. J. Biochem. Mol. Biol. 23, 66–77.
Braicu, C., Pilecki, V., Balacescu, O., Irmine, A., Berindan, I.N., 2011. The relationships between biological activities and structure of flavan-3-ols. Int. J. Mol. Struct. 12, 9342–9353.
Brewer, M.S., 2011. Natural antioxidants: sources, compounds, mechanisms of action, and potential applications. Compr. Rev. Food Sc. Technol. 10, 221–247.
Brett, A.M.O., Ghica, M.E., 2003. Electrochemical oxidation of quercetin. Electroanalysis 22, 1745–1750.
Butkovic, V., Klasinc, L., Bors, W., 2004. Kinetic study of flavonoid reactions with stable radicals. J. Agric. Food Chem. 52, 2816–2820.
Choe, E., Min, D.B., 2009. Mechanisms of antioxidants in the oxidation of foods. Compr. Rev. Food Sci. Food Saf. 8, 345–358.
Chaturvedi, R.K., Beal, M.F., 2013. Mitochondrial diseases of the brain. Free Radic. Biol. Med. 63, 1–29.
Chedea, V.S., Braicu, C., Socaciu, C., 2010. Antioxidant/prooxidant activity of a polyphenolic grape seed extract. Food Chem. 121, 132–139.
Cheng, I.F., Breen, K., 2000. On the ability of four flavonoids, baicilein, luteolin, naringenin, and quercetin, to suppress the Fenton reaction of the iron-ATP complex. Biometals 13, 77–83.
Cheynier, V., Comte, G., Davies, K.M., Lattanzio, V., Martens, S., 2013. Plant phenolics: recent advances on their biosynthesis, genetics, and ecophysiology. Plant Physiol. Biochem. 72, 1–20.
Chobot, V., Hadacek, F., 2011. Exploration of pro-oxidant and antioxidant activities of the flavonoid myricetin. Redox Rep. 16, 242–247.
Constantin, R.P., Nascimento, G.S., Constantin, R.P., Salgueiro, C.L., Bracht, A., Ishii-Iwamoto, E.L., Yamamoto, N.S., Constantin, J., 2013. Citrus flavanones affect hepatic fatty acid oxidation in rats by acting as prooxidant agents. BioMed Res. Int. 1–12 2013.
Craft, B.D., Kerrihard, A.L., Amarowicz, R., Pegg, R.B., 2012. Phenol-based antioxidants and the *in Vitro* methods used for their assessment. Compr. Rev. Food Sci. Food Saf. 11, 148–173.
Cuvelier, M.E., Richard, H., Berset, C., 1992. Comparison of the antioxidative activity of some acid-phenols: structure –activity relationship. Biosci. Biotechnol. Biochem. 56, 324–325.
Dawidowicz, A.L., Olszowy, M., 2010. Influence of some experimental variables and matrix components in the determination of antioxidant properties by β-carotene bleaching assay: experiments with BHT used as standard antioxidant. Eur. Food Res. Technol. 231, 835–840.
Dawidowicz, A.L., Olszowy, M., 2011. Antioxidant properties of BHT estimated by ABTS assay in systems differing in pH or metal ion or water concentration. Eur. Food Res. Technol. 232, 837–842.
Dawidowicz, A.L., Olszowy, M., 2012. Mechanism change in estimating of antioxidant activity of phenolic compounds. Talanta 97, 312–317.
Dawidowicz, A.L., Wianowska, D., Olszowy, M., 2012. On practical problems in estimation of antioxidant activity of compounds by DPPH method (Problems in estimation of antioxidant activity). Food Chem. 131, 1037–1043.
Dawidowicz, A.L., Olszowy, M., 2013. The importance of solvent type in estimating antioxidant properties of phenolic compounds by ABTS assay. Eur. Food Res. Technol. 236, 1099–1105.
Dawidowicz, A.L., Olszowy, M., 2015. Depletion/protection of β-carotene in estimating antioxidant activity by β-carotene bleaching assay. J. Food Sci. Technol. 52, 7321–7328.
Dawidowicz, A.L., Olszowy, M., Jóźwik-Dolęba, M., 2015a. Antagonistic antioxidant effect in butylated hydroxytoluene/butylated hydroxyanisole mixture. J. Food Process. Preserv. 39, 2240–2248.
Dawidowicz, A.L., Olszowy, M., Jóźwik-Dolęba, M., 2015b. Importance of solvent association in the estimation of antioxidant properties of phenolic compounds by DPPH method. J. Food Sci. Technol. 52, 4523–4529.
De Oliveira-Roberth, A., Santos, D.I.V., Cordeiro, D.D., Lino, F.M.A., Bara, M.T.F., Gil, E.S., 2012. Voltammetric determination of rutin at screen-printed carbon disposable electrodes. Cent. Eur. J. Chem. 10 (5), 1609–1616.
Dreher, D., Junod, A.F., 1996. Role of oxygen free radicals in cancer development. Eur. J. Cancer 32, 30–38.
Eghbaliferiz, S., Iranshahi, M., 2016. Prooxidant activity of polyphenols, flavonoids, anthocyanins and carotenoids: updated review of mechanism and catalyzing metals. Phytother. Res. 30, 1379–1391.
Fernandez, M.T., Mira, M.R., Florêncio, M.H., Jennings, K.R., 2002. Iron and copper chelation by flavonoids: an electrospray mass spectrometry study. J. Inorg. Biochem. 92, 105–111.
Filipović, M., Marković, Z., Dorović, J., Dimitrić Marković, J., Lučić, B., Amić, D., 2015. QSAR of the free radical scavenging potency of selected hydroxybenzoic acids and simple phenolics. Compt. Rendus Chem. 18, 492–498.
Finotti, E., Majo, D.D., 2003. Influence of solvents on the antioxidant property of flavonoids. Mol. Nutr. Food Res. 47, 186–187.
Foti, M.C., 2007. Antioxidant properties of phenols. J. Pharm. Pharmacol. 59, 1673–1685.
Foti, M.C., Daquino, C., Dilabio, G.A., Ingold, K.U., 2011. Kinetics of the oxidation of quercetin by 2,2-Diphenyl-1-picrylhydrazyl (dpph˙). Org. Lett. 13, 4826–4829.
Foti, M.C., Ruberto, G., 2001. Kinetic solvent effects on phenolic antioxidants determined by spectrophotometric measurements. J. Agric. Food Chem. 49, 342–348.
Freeman, B.L., Eggett, D.L., Parker, T.L., 2010. Synergistic and antagonistic interactions of phenolic compounds found in navel oranges. J. Food Sci. 75, 570–576.
Friaa, O., Brault, D., 2006. Kinetics of the reaction between the antioxidant Trolox and the free radical DPPH in semi-aqueous solution. Org. Biomol. Chem. 4, 2417–2423.
Galano, A., Alvarez-Idaboy, J.R., Francisco-Márquez, M., Medina, M.E., 2012. A quantum chemical study on the free radical scavenging activity of tyrosol and hydroxytyrosol. Theor. Chem. Acc. 131, 1173–1185.
Galano, A., Castañeda-Arriaga, R., Pérez-González, A., Tan, D.X., Reiter, R.J., 2016. Phenolic melatonin-related compounds: their role as chemical protectors against oxidative stress. Molecules 21, 1442–1484.
Galano, A., Muñoz-Rugeles, L., Alvarez-Idaboy, J.R., Bao, J.L., Truhlar, D.G., 2015. Hydrogen abstraction reactions from phenolic compounds by peroxyl radicals: multireference character and density functional theory rate constants. J. Phys. Chem. 120, 4634–4642.
Gil, E.S., Couto, R.O., 2013. Flavonoid electrochemistry: a review on the electroanalytical applications. Braz. J. Pharmacogn. 23, 542–558.
Gülçin, I., 2006. Antioxidant activity of caffeic acid (3,4 dihydroxycinnamic acid). Toxicology 217, 213–220.
Gupta, V.K., Sharma, S.K., 2006. Plants as natural antioxidants. Nat. Product. Radiance 5, 326–334.
Halliwell, B., 2008. Are polyphenols antioxidants or pro-oxidants? What do we learn from cell culture and *in vivo* studies? Arch. Biochem. Biophys. 476, 107–112.
Han, X., Shen, T., Lou, H., 2007. Dietary polyphenols and their biological significance. Int. J. Mol. Sci. 8, 950–988.
Hasima, N., Ozpolat, B., 2014. Regulation of autophagy by polyphenolic compounds as a potential therapeutic strategy for cancer. Cell Death Dis. 5, 1–13.
Hoelz, L.V.B., Horta, B.A.C., Araújo, J.Q., Albuquerque, M.G., Alencastro, R.B., Silva, J.F.M., 2010. Quantitative structure-activity relationships of antioxidant phenolic compounds. J. Chem. Pharm. Res. 2 (5), 291–306.
Hotta, H., Sakamoto, H., Nagano, S., Osakai, T., Tsujino, Y., 2001. Unusually large numbers of electrons for the oxidation of polyphenolic antioxidants. Biochimica et Biphysica Acta 1526, 159–167.
Inácio, M.C., Moraes, R.M., Mendonça, P.C., Morel, L.J.F., França, S.C., Bertoni, B.V., Pereira, A.M.S., 2013. Phenolic compounds influence seed dormancy of *Palicourea rigida* H.B.K. (Rubiaceae), a medicinal plant of the Brazilian Savannah. Am. J. Plant Sci. 4, 129–133.
Iuga, C., Alvarez-Idaboy, J.R., Russo, N., 2012. Antioxidant activity of *trans*-resveratrol toward hydroxyl and hydroperoxyl radicals: a quantum chemical and computational kinetics study. J. Org. Chem. 77, 3868–3877.
Jeremić, S., Radenković, S., Filipović, M., Antić, M., Amić, A., Marković, Z., 2017. Importance of hydrogen bonding and aromaticity indices in QSAR modeling of the antioxidative capacity of selected (poly)phenolic antioxidants. J. Mol. Graph. Model. 72, 240–245.
Kähkönen, M.P., Heinonen, M., 2003. Antioxidant activity of anthocyanins and their aglycones. J. Agric. Food Chem. 51, 628–633.
Krysztofiak, A., Krajka-Kuźniak, V., 2015. When defense becomes dangerous – transcription factor Nrf2 and cancer. Postępy Higieny Medycyny Doświadczalnej 69, 140–152.
Lambert, J.D., Elias, R.J., 2010. The antioxidant and pro-oxidant activities of green tea polyphenols: a role in cancer. Arch. Biochem. Biophys. 501, 65–72.
León-Carmona, J.R., Alvarez-Idaboy, J.R., Galano, A., 2012. On the peroxyl scavenging activity of hydroxycinnamic acid derivatives: mechanisms, kinetics, and importance of the acid–base equilibrium. Phys. Chem. Chem. Phys. 14, 12534–12543.
León-González, A.J., Auger, C., Schini-Kerth, V.B., 2015. Pro-oxidant activity of polyphenols and its implication on cancer chemoprevention and chemotheraphy. Biochem. Pharmacol. 98, 371–380.
Leopoldini, M., Chiodo, S.G., Russo, N., Toscano, M., 2011a. Detailed investigation of the OH radical quenching by natural antioxidant caffeic acid studied by quantum mechanical models. J. Chem. Theory Comput. 7, 4218–4233.
Leopoldini, M., Marino, T., Russo, N., Toscano, M., 2004. Antioxidant properties of phenolic Compounds: H-atom versus electron transfer mechanism. J. Phys. Chem. A 108, 4916–4922.
Leopoldini, M., Rondinelli, F., Russo, N., Toscano, M., 2010. Pyranoanthocyanins: a theoretical investigation on their antioxidant activity. J. Agric. Food Chem. 58, 8862–8871.
Leopoldini, M., Russo, N., Toscano, M., 2011b. The molecular basis of working mechanism of natural polyphenolic antioxidants. Food Chem. 125, 288–306.
Litwinienko, G., Ingold, K.U., 2004. Abnormal solvent effects on hydrogen atom abstraction. 2. Resolution of the curcumin antioxidant controversy. The Role of Sequential Proton Loss Electron Transfer. J. Org. Chem. 69, 5888–5896.
Litwinienko, G., Ingold, K.U., 2007. Solvent effects on the rates and mechanisms of reaction of phenols with free radicals. Acc. Chem. Res. 40, 222–230.
Liu, Y.R., Li, W.G., Chen, L.F., Xiao, B.K., Yang, J.Y., Yang, L., Zhang, C.G., Huang, R.Q., Dong, J.X., 2014. ABTS + scavenging potency of selected flavonols from Hypericum perforatum L. by HPLC-ESI/MS QQQ: reaction observation, adduct characterization and scavenging activity determination. Food Res. Int. 58, 47–58.
Lobo, V., Patil, A., Phatak, A., Chandra, N., 2010. Free radicals, antioxidants and functional foods: impact on human health. Pharmacogn. Rev. 4, 118–126.
Lü, J.M., Lin, P.H., Yao, Q., Chen, Ch, 2010. Chemical and molecular mechanism of

antioxidants: experimental approaches and model systems. Mol. Med. 14, 840–860.
Macikova, P., Halouzka, V., Hrbac, J., Bartak, P., Skopalova, J., 2012. Electrochemical behavior and determination of rutin on modified carbon paste electrodes. Sci. World J. 1–9 2012.
Marino, T., Galano, A., Russo, N., 2014. Radical scavenging ability of gallic acid toward OH and OOH radicals. Reaction mechanism and rate constants from the density functional theory. J. Phys. Chem. B 118, 10380–10389.
Marković, Z., Amić, D., Milenković, D., Dimitrić-Marković, J.M., Marković, S., 2013. Examination of the chemical behavior of the quercetin radical cation towards some bases. Phys. Chem. Chem. Phys. 15, 7370–7378.
Marković, Z., Dorović, J., Dimitrić Marković, J.M., Bioćanić, R., Amić, D., 2016. Comparative density functional study of antioxidative activity of the hydroxybenzoic acids and their anions. Turk. J. Chem. 40, 499–509.
Martín, M.Á., Serrano, A.B.G., Ramos, S., Pulido, M.I., Bravo, L., Goya, L., 2010. Cocoa flavonoids up-regulate antioxidant enzyme activity via the ERK1/2 pathway to protect against oxidative stress-induced apoptosis in HepG2 cells. JNB (J. Nutr. Biochem.) 21, 196–205.
Masella, R., Vari, R., D'Archivio, M., Di Benedetto, R., Matarrese, P., Malorni, W., Scazzocchio, B., Giovannini, C., 2004. Extra virgin olive oil biophenols inhibit cell-mediated oxidation of LDL by increasing the mRNA transcription of glutathione-related enzymes. J. Nutr. 134, 785–791.
Mazzone, G., Galano, A., Alvarez-Idaboy, J.R., Russo, N., 2016. Coumarin-Chalcone hybrids as peroxyl radicals scavengers: kinetics and mechanisms. J. Chem. Inf. Model. 56, 662–670.
Milenković, D., Dorović, J., Jeremić, S., Dmitrić Marković, J.M., Avdović, E.H., Marković, Z., 2017. Free radical scavenging potency of dihydroxybenzoic acids. J. Chem. 1–9 2017.
Mira, L., Fernandez, M.T., Santos, M., Rocha, R., Florêncio, M.F., Jennings, K.R., 2002. Interactions of flavonoids with iron and copper ions: a mechanism for their antioxidant activity. Free Radic. Res. 36, 1199–1208.
Musialik, M., Kuźmicz, R., Pawłowski, T.S., Litwinienko, G., 2009. Acidity of hydroxyl groups: an overlooked influence on antiradical properties of flavonoids. J. Org. Chem. 74, 2699–2709.
Ndhlala, A.R., Moyo, M., Van Staden, J., 2010. Natural antioxidants: fascinating or mythical biomolecules? Molecules 15, 6905–6930.
Olszowy, M., Dawidowicz, A.L., 2016. Essential oils as antioxidants: their evaluation by DPPH, ABTS, FRAP, CUPRAC, and β-carotene bleaching methods. Monatshefte Chem. 147, 2083–2091.
Olszowy, M., Dawidowicz, A.L., 2018. It is possible to use the DPPH and ABTS methods for relaible estimation of antioxidant power of colored compounds? Chem. Pap. 72, 393–400.
Osman, A.M., Wong, K.K.Y., Fernyhough, A., 2006. ABTS radical-driven oxidation of polyphenols: isolation and structural elucidation of covalent adducts. Biochem. Biophys. Res. Commun. 346, 321–329.
Osman, A.M., 2011. Multiple pathways of the reaction of 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) with (+)-catechin: evidence for the formation of a covalent adduct between DPPH and the oxidized form of the polyphenol. Biochem. Biophys. Res. Commun. 412, 473–478.
Packer, L., Sies, H., 2001. Flavonoids and Other Polyphenols. Academic Press, London.
Pandey, K.B., Rizvi, S.I., 2009. Plant polyphenols as dietary antioxidants in human health and disease. Oxid. Med. Cell. Longev. 2, 270–278.
Pannala, A.S., Chan, T.S., O'Brien, P.J., Rice-Evans, C.A., 2001. Flavonoid B-ring chemistry and antioxidant activity; fast reaction kinetics. Biochem. Biophys. Res. Commun. 282, 1161–1168.
Perez-Gonzalez, A., Rebollar-Zepeda, A.M., Leon-Carmona, J.R., Galano, A., 2012. Reactivity indexes and O-H bond dissociation energies of a large series of polyphenols: implications for their free radical scavenging activity. J. Mex. Chem. Soc. 51, 241–248.
Pham-Huy, L.A., He, H., Pham-Huy, Ch, 2008. Free radicals, antioxidants in disease and health. Int. J. Biomed. Sci. 4, 89–96.
Piazzon, A., Vrhovesk, U., Masuero, D., Mattivi, F., Mandoj, F., Nardini, M., 2012. Antioxidant activity of phenolic acids and their metabolites: synthesis and antioxidant properties of the sulfate derivatives of ferulic and caffeic acids and of the acyl glucuronide of ferulic acid. J. Agric. Food Chem. 60, 12312–12323.
Pietta, P.G., 2000. Flavonoids as antioxidants. J. Nat. Prod. 63, 1035–1042.
Pinelo, M., Manzocco, L., Nuñez, M.J., Nicoli, M.C., 2004. Interaction among phenols in food fortification: negative synergism on antioxidant capacity. J. Agric. Food Chem. 52, 1177–1180.
Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., Squadrito, F., Altavilla, D., Bitto, A., 2017. Oxidative stress: harms and Benefits for human health. Oxid. Med. Cell. Longev. 2017 (8416763), 1–13.
Polumbryk, M., Ivanov, S., Polumbryk, O., 2013. Antioxidants in food systems. Mechanism of action. Ukr. J. Food Sci. 1, 15–40.
Procházková, D., Boušová, I., Wilhelmová, N., 2011. Antioxidant and prooxidant properties of flavonoids. Fitoterapia 82, 513–523.
Rezk, B.M., Haenen, G.R.M.M., Van Der Vijgh, W.J.F., Bast, A., 2002. The antioxidant activity of phloretin: the disclosure of a new antioxidant pharmacophore in flavonoids. Biochem. Biophys. Res. Commun. 295, 9–13.
Rice-Evans, C., Miller, N.J., Paganga, G., 1996. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radical Biol. Med. 20, 933–956.
Roginsky, V., 2003. Chain-breaking antioxidant activity of natural polyphenols as determined during the chain oxidation of methyl linoleate in Triton X-100 micelles. Arch. Biochem. Biophys. 414, 261–270.
Santos, J.S., Brizola, V.R.F., Granato, D., 2017. High-throughput assay comparison and standardization for metal chelating capacity screening: a proposal and application. Food Chem. 214, 515–522.
Shahidi, F., Zhong, Y., 2015. Measurement of antioxidant activity. J. Funct. Food 18, 757–781.
Shalaby, E.A., Shanab, S.M.M., 2013. Antioxidant compounds, assays of determination and mode action. Afr. J. Pharm. Pharmacol. 7, 528–539.
Silva, A.M., Vidal-Novoa, A., Batista-González, A.E., Pinto, J.R., Mancini, D.A.P., Reina-Urquijo, W., Mancini-Filho, J., 2012. In vivo and in vitro antioxidant activity and hepatoprotective properties of polyphenols from Halimeda opuntia (Linnaeus) Lamouroux. Redox Rep. 17, 47–53.
Simić, A., Manojlović, D., Segan, D., Todorović, M., 2007. Electrochemical behavior and antioxidant and prooxidant activity of natural phenolics. Molecules 12, 2327–2340.
Singh, R.P., Sharad, S., Kapur, S., 2004. Free radicals and oxidative stress in neurodegenerative diseases: relevance of dietary antioxidants. J. Indian Acad. Clin. Med. 5, 218–225.
Son, S.M., 2012. Reactive oxygen and nitrogen species in pathogenesis of vascular complication of diabetes. J. Diabetes Metab. 36, 190–198.
Sousa, R.W., Da Rocha, C., Cardoso, C.L., Silva, S.D.H., Zanoni, B.M.V., 2004. Determination of the relative contribution of phenolic antioxidants in orange juice by voltammetric methods. J. Food Compos. Anal. 17, 619–633.
Stepanić, V., Trošelj, K.G., Lučić, B., Marković, Z., Amić, D., 2013. Bond dissociation free energy as a general parameter for flavonoid radical scavenging activity. Food Chem. 141, 1562–1570.
Symonowicz, M., Kolanek, M., 2012. Flavonoids and their properties to form chelate complexes. Biotechnol. Food Sci. 76, 35–41.
Tai, A., Ohno, A., Ito, H., 2016. Isolation and characterization of the 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical cation-scavenging reaction products of arbutin. J. Agric. Food Chem. 64, 7285–7290.
Thavasi, V., Bettens, R.P.A., Leong, L.P., 2009. Temperature and solvent effects on radical scavenging ability of phenols. J. Phys. Chem. A 113, 3068–3077.
Touriño, S., Lizárraga, D., Carreras, A., Matitio, C., Ugartondo, V., Mitjans, M., Centelles, J.J., Vinardell, M.P., Juliá, L., Cascante, M., Torres, J.L., 2008. Antioxidant/prooxidant effects of bioactive polyphenolics. Electron. J. Environ. Agric. Food Chem. 7, 3348–3352.
Trabelsi, S.K., Tahar, N.B., Abdelhedi, R., 2004. Electrochemical behavior of caffeic acid. Electrochim. Acta 49, 1647–1654.
Tsimogiannis, D.I., Oreopoulou, V., 2004. Free radical scavenging and antioxidant activity of 5,7,3′,4′-hydroxy-substituted flavonoids. Innov. Food Sci. Emerg. Technol. 5, 523–528.
Vellosa, J.C.R., Regasini, L.O., Khalil, N.M., Bolzani, V.S., Khalil, O.A.K., Manente, F.A., Netto, H.P., Oliveira, O.M.M.F., 2011. Antioxidant and cytotoxic studies for kaempferol, quercetin and isoquercitrin. Ecletica Quim. 36, 7–20.
Villaňo, D., Fernández-Pachón, M.S., Troncoso, A.M., García-Parrilla, M.C., 2005. Comparison of antioxidant activity of wine phenolic compounds and metabolites in vitro. Anal. Chim. Acta 538, 391–398.
Wojdyło, A., Oszmiański, J., Czemerys, R., 2007. Antioxidant activity and phenolic compounds in 32 selected herbs. Food Chem. 105, 940–949.
Yeh, C.T., Yen, G.C., 2006. Induction of hepatic antioxidant enzymes by phenolic acids in rats is accompanied by increased levels of multidrug resistance–associated protein 3 mRNA expression. J. Nutr. 136, 11–15.
Yordi, E.G., Pérezi, E.M., Matos, M.J., Villares, E.U., 2012. Antioxidant and pro-oxidant effects of polyphenolic compounds and structure-activity relationship evidence. In: Jaouad, Bouayed, Torsten, Bohn (Eds.), Chapter in Book Nutrition, Well-Being and Health.
Yoshino, M., Murakami, K., 1998. Interaction of iron with polyphenolic compounds: application to antioxidant characterization. Anal. Biochem. 257, 40–44.
Zheng, L.-F., Dai, F., Zhou, B., Yang, L., Liu, Z.-L., 2008. Prooxidant activity of hydroxycinnamic acids on DNA damage in the presence of Cu (II) ions: mechanism and structure-activity relationship. Food Chem. Toxicol. 46, 149–156.
Zhou, L., Elias, R.J., 2013. Antioxidant and pro-oxidant activity of (−)-epigallocatechin-3-gallate in food emulsion: influence of pH and phenolic concentration. Food Chem. 138, 1503–1509.
Zielińska, D., Szawara-Nowak, D., Zieliński, H., 2010. Determination of the antioxidant activity of rutin and its contribution to the antioxidant capacity of diversified buckwheat origin material by updated analytical strategies. Pol. J. Food Nutr. Sci. 60, 315–321.