Current view on the assessment of antioxidant and antiradical activities: A mini review

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Abstract. The main problems in assessing the antioxidant properties of plant biologically active compounds are discussed in this review. Antioxidant potential should be considered as a combination of antioxidant and antiradical activities, since antiradical activity is part of the antioxidant activity and does not always coincide with antioxidant activity. The mechanisms of action and the existing experimental and computational methods for their evaluation were reviewed. Methods like FRAP, CUPRAC etc. could be used for assessment of antioxidant activity of plant compounds, but it is necessary to perform studies on cell cultures or laboratory animals in order to determine mechanisms of action on the antioxidant system of a living organism. The current methodological approaches for studying antiradical activity and its mechanisms include experimental methods such as DPPH, ABTS and ORAC, and computational methods based on density functional theory. The main thermodynamic parameters for evaluating antiradical mechanisms (HAT, SET-PT and SPLET) are the bond dissociation enthalpy, ionization potential, proton dissociation enthalpy, proton affinity, and electron transfer enthalpy, among others. The existing approaches for determining the antiradical mechanisms of antioxidants are quite informative, but can still cannot predict or determine by in vitro methods the antioxidant mechanism of these compounds in organisms consisting of many complex individual systems.

1. Introduction

The study of substances with antioxidant properties is one of the relevant scientific areas. From 2015 to 2021, 199,681 articles were published in the international database Scopus for the query “antioxidant”. However, the terminology, research methods, and expression of the obtained data are still not uniform, which makes it difficult to interpret and compare the results of the research [1]. Thus, the term “antioxidant” has several definitions, for example, antioxidants are compounds that inhibit oxidation, a chemical reaction that can produce free radicals and chain reactions that may damage the cells of organisms. Halliwell and Gutteridge proposed a broader definition of antioxidants as “any substance that, when present at low concentration compared with those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate”. Moreover, the term “oxidizable substrate” includes all organic and many inorganic molecules present in vivo [2].

On the other hand, the authors used different terms to describe the antioxidant properties, which are characterized by a wide variety and have different frequency of use. The most popular term is
“antioxidant activity”, while the terms “antioxidant capacity”, “antioxidant content”, “antioxidant power”, “antioxidant ability” and “antioxidant potential” are used much less often [1]. Despite the prevalence of the term “antioxidant activity”, its appropriateness depends on the chosen research methods. The authors often describe the “antioxidant activity” (AOA) of the studied samples, but in fact they studied the “antiradical activity” (ARA).

The use of a specific term to describe the antioxidant potential of research objects depends on the methods and approaches that have been used to study these properties. In addition, for more accurate and comprehensive determination of the antioxidant properties of plant samples, it is necessary to use at least two methods. Thus, the aim of this study was to review the existing approaches and methods for assessing the antioxidant potential of substances of plant origin, taking into account the difference of concepts “antioxidant activity” and “antiradical activity”.

2. Antioxidative mechanisms

Antioxidant and antiradical activities characterize the ability of a substance or mixture of substances to act as an antioxidant and reduce the negative effects of oxidative reactions on cells, organs, the body, and even food. However, ARA and AOA describe different principles of activity; therefore, these concepts should be distinguished [3]. ARA characterizes the ability of compounds to react with free radicals (in a single free radical reaction), while AOA describes the ability of substance to inhibit the process of oxidation, which usually involves many different reactions, such as lipid peroxidation [4].

Antioxidant mechanisms are ways of inhibiting oxidative reactions and processes occurring in complex biological systems. These mechanisms include regulating the activity of enzymes by inhibiting the production of oxidases, which promote the generation of reactive oxygen species (ROS), or enhancing antioxidant enzyme activity, in particular, the activity of superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT), glutathione reductase (GR) and glutathione thiotransferase (GST) [5,6]. The ability of a compound to interact with the free metal ions (iron and copper) with the formation of inactive complexes of these metals also belongs to antioxidant mechanisms [5], does the influence of substances on cell antioxidant responses according to different pathways [5,7]. Despite numerous approaches to the study of antioxidant activity, there is no universal method that allows prediction of the mechanism by which a substance will exhibit antioxidant activity. Therefore, different research methods are carried out depending on the purpose of the work.

Antiradical activity is more clear and encompasses three generally accepted mechanisms of action against free radicals: hydrogen atom transfer (HAT) (1), single-electron transfer followed by proton transfer (SET-PT) (2, 3) and sequential proton loss electron transfer (SPLET) (4-6) [8–10]. SET-PT and SPLET mechanisms are often unified into single electron transfer (SET) [11].

\[
\begin{align*}
    \text{ArOH} + R^- \rightarrow \text{ArO}^- + \text{RH} & \quad (1) \\
    \text{ArOH} + R^- \rightarrow \text{ArOH}^{-}^* + R^- & \quad (2) \\
    \text{ArOH}^{-}^* + R^- \rightarrow \text{ArO}^- + \text{RH} & \quad (3) \\
    \text{ArOH} \rightarrow \text{ArO}^- + H^+ & \quad (4) \\
    \text{ArO}^- + R^- \rightarrow \text{ArO}^- + R^- & \quad (5) \\
    R^- + H^+ \rightarrow \text{RH} & \quad (6)
\end{align*}
\]

According to these equations, all mechanisms are described for compounds that have an –OH group in the structure. In addition, each mechanism produces a new radical (ArO’), which is more stable and less reactive than the original free radical (R’) [8]. Antiradical mechanisms are characterized by thermodynamic parameters: bond dissociation enthalpy (BDE) accompanied reaction (1); ionization potential (IP) accompanied reaction (2), proton dissociation enthalpy (PDE) accompanied reaction (3); proton affinity (PA) accompanied reaction (4); and the electron transfer enthalpy (ETE) accompanied reaction (5) [8]. Summarizing, antiradical activity has specific parameters for determination, while antioxidant activity does not have such certain assessment criteria. Thus, it is necessary to clearly
distinguish antiradical activity from antioxidant activity, because these properties do not always coincide [3,4].

3. Methods for evaluating the effect of antioxidants

There are a wide range of methods for comprehensive study the antioxidant properties of compounds or mixtures of substances. However, in the case of dividing the antioxidant potential into antioxidant and anti-radical activity, it is necessary to clearly understand that the choice of method and approach should be carried out relative to the goals set. Biological methods, which include cell cultures, laboratory animals and human studies, are used for studies of antioxidant activity. Biological methods are very expensive and take a lot of time [3], and therefore, such chemical methods as ferric reducing antioxidant power (FRAP), cupric reducing antioxidant capacity (CUPRAC) etc. are more often applied for AOA investigation [12]. The FRAP method is based on the reduction of a ferric (III) 2,4,6-tripyridyl-s-triazine complex by antioxidants to ferric (II) in accordance with the reaction (7) [12].

\[
Fe(TPTZ)_2^{3+} + ArOH \rightarrow Fe(TPTZ)_2^{2+} + ArO^- + H^+
\]  

The CUPRAC method is identical to the FRAP method and based on the reduction of a cupric neocuproine complex (Cu(II)–Nc) by antioxidants to the cuprous form (Cu(I)–Nc) [12]. These methods significantly limit researchers, since they only allow the ability of samples to reduce metals to be evaluated, but they are fast, cheap and easily reproducible, which makes them effective indicators of the antioxidant system condition in oxidative stress and related studies [3].

Test systems, including biological, chemical and biochemical methods of analysis, are more effective in studying the antioxidant activity. Kwanjit Danwilai et al. [13] studied the antioxidant activity of ginger extract by measuring in patients indicators such as the activities of SOD and CAT and levels of glutathione peroxidase, total glutathione (GSH/GSSG), lipid peroxidation products detected as malondialdehyde (MDA) and NO_2^-/NO_3^-.. Biswajit Podder et al. [14] assessed antioxidant activity of sea buckthorn extract by measuring the viability of A549 cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and lactate dehydrogenase (LDH). We also investigated the antioxidant activity of onion husk extract by measuring the activities of SOD and CAT, the concentration of total glutathione and malondialdehyde, and ferric reducing antioxidant power in blood plasma, brain, and liver in aging laboratory animals [15]. The results of our research clearly demonstrated the effectiveness of a system approach.

Currently, there are a lot of methods for analyzing antiradical activity, but scientists mostly use generally accepted and widely applied methods. Thus, the determination of antiradical activity is most often investigated using the ABTS, DPPH, and oxygen radical absorbent capacity (ORAC) methods, which use stable free radicals and are based on measuring the ability of an antioxidant to suppress these free radicals. All methods with a stable free radical provide information about the activity of trapping radicals, although in many cases this activity does not correspond to the antioxidant activity. It is necessary to carry out research on a real product or in a live system in order to get information about the actual antioxidant activity in relation to lipids or food preservation [4].

According to the ABTS method, pre-formed dark green stable free radical 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt radical cation (ABTS^+) is reduced by a compound [3,16]. The obvious disadvantage of this method is the random nature of the reactions of the free radical, which is a non-physiological free radical [4].

According to the DPPH method, the stable radical 1,1-diphenyl-2-picrylhydrazyl loses its dark purple colour when interacting with antioxidants. The antiradical activity of tested compounds is expressed as a relative or absolute decrease of the concentration of DPPH or as EC50 (concentration of a compound decreasing the absorbance of a DPPH solution by 50 %) [4,9,17]. Despite the prevalence of the method using the DPPH' radical, it has been suggested that it is preferable to use the O-centred stable galvinoxyl (II) radical, which is more closely related to physiologically active oxygen radicals than DPPH, to measure antiradical activity. Gunars Tirzitis et al. [4] mentioned that in some cases, the DPPH test gives
incorrect results, and therefore, recommendations for the correct application of the method were proposed.

The ORAC method is another modern method for determining ARA [18]. This method is based on the inhibition of probe oxidation caused by peroxyl radicals, where peroxyl radicals are formed as a result of the thermal decomposition of azo-compounds, such as 2,2-azobis (2-amidino-propane) dihydrochloride (AAPH) [18,19]. The decomposition of the fluorescent probe is slowed down in the reaction mixture when the antioxidants react with peroxyl radicals [20]. Despite its high sensitivity, the ORAC method is less common than ABTS and DPPH, due to more specific equipment being required. It is worth noting that scientists often use combinations of methods to characterize antiradical activity, since there is no official standardized method [21].

Researchers discussed that, based on the chemical methods ABTS, DPPH and ORAC, it is possible to assume by what mechanism the antioxidant acted. Most researchers claimed that the use of the ORAC method allows determination of the antioxidants acting according the HAT mechanism [18,22,23], while the FRAP method determines antioxidants according to the SET mechanism [22,23]. However, in the case of the ABTS and DPPH methods, there are often conflicting statements about the mechanism to which they correspond. Some scientists believe that the use of the ABTS and DPPH methods allows determination of the antioxidant acting according to the HAT mechanism [3,24] while others argued that the ABTS and DPPH methods, as well as the FRAP analysis, assessing antioxidant acting according to the SET mechanism [18,23], since basic/acid solutions can promote the deprotonating/protonating of susceptible molecules [23,25]. Opposed views arise because the reaction of antioxidant with free radical is influenced by various factors. For example, the reaction with DPPH is significantly affected by the absolute and relative concentrations of DPPH and antioxidants, solvents, hydrogen bond strength, temperature, time, and pH [9,26]. Moreover, the lack of standardization in sample preparation, reaction conditions, analytical protocols, and expression of antioxidant activity makes it difficult to compare results obtained in different laboratories. In addition, the biological activity of compounds depends on the structure of the molecule, the medium and conditions of the reactions, the combination with other compounds, solubility, absorption, etc. Antiradical activity of phenolic antioxidants strongly depends on their structural characteristics [9,27].

4. Computational methods for evaluating the antioxidant potential
Plants are the richest source of natural antioxidants. Plants contain a great variety of such substances in the classes of phenolic compounds and flavonoids, while tannins, carotenoids, anthocyanins, diterpenes, terpenoids, etc. are present in smaller amounts. Scientists can successfully combine analytical and computational methods for more accurate determination of the anti-radical mechanism of action of antioxidants after the isolation, separation and identification of plant compounds by experimental methods. There are already many studies devoted to the investigation of the antioxidant properties of natural compounds, using test systems that include experimental and computational methods of analysis.

Chen et al. [9] assessed relationships between the structure, thermodynamics, and antiradical activity of 20 natural phenolic acids and their derivatives using DPPH scavenging assay, density functional theory (DFT) calculations at the B3LYP/6-311++G(d,p) levels of theory, and quantitative structure-activity relationship (QSAR) modelling. It was observed, that the C=O or C=C in COOH, COOR, C=CCOOH and C=CCOOR groups, and orthophenolic functionalities enhanced antiradical activity, while the presence of the single OH in the ortho position of the COOH group reduced antiradical activity. In addition, FR scavenging in the gas phase and benzene is most probable by the HAT mechanism, whereas in water and ethanol, the most likely mechanism is by SPLET, according to thermodynamics principles. Similar results were obtained by Milenković et al. [8]. Thermodynamic parameters such as BDE, IP, and PA were calculated for certain dihydroxybenzoic acids in nonpolar (benzene and pentylethanoate) and polar (water) solvents. The researchers found the HAT mechanism for dihydroxybenzoic acids was more probable in benzene, but in water the SPLET mechanism ruled; under the studied conditions, phenolic acids did not exhibit antiradical properties by the SET-PT mechanism.
Spiegel et al. [3] studied influence of the structure on the antioxidant potential of 22 phenolic acids. According to the results of FRAP and DFT, mono hydroxylated compounds and compounds with two hydroxyl groups in meta position to each other expressed the lowest antioxidant properties, while compounds with two or more hydroxyl groups in ortho or para position to each other demonstrated the highest antioxidant properties. Chen et al. [28] suggested that all antiradical mechanisms, HAT, SET-PT and SPLET, can occur in the reaction of phenolic compounds with DPPH, while the FRAP method is characterized only by the SPLET mechanism. This hypothesis is based on data from DPPH and FRAP analyses combined with calculations of five thermodynamic parameters for 18 phenolic acids. Thermodynamic parameters were calculated using DFT with the B3LYP/UB3LYP functional and 6–311++G (d, p) basis set. A number of other similar studies evaluated the antioxidant properties of flavonoid compounds [29,30], phenolic compounds [30], natural hydroxycinnamic acids [31], quercetin and its glucosides from propolis [32], chlorogenic acid [33], quercetin and morin [34].

Plant phenolic compounds can scavenge FR using three competitive mechanisms (HAT, SET-PT and SPLET), but the predominance of a particular mechanism depends on the structure of the antioxidant, the reaction conditions, and the solvent. The antioxidant capacity of phenolic compounds is significantly reduced when using a solvent that is prone to the formation of hydrogen bonds with phenolic compounds. For example, alcohols have a double effect on the reaction rate between the phenol and the peroxyl radical. On the one hand, alcohols act as acceptors of hydrogen bonds, and on the other hand, they promote the ionization of phenols to anionic phenoxides, which can react rapidly with peroxyl radicals through electron transfer. The general effect of the solvent on the antioxidant potential of phenolic compounds largely depends on the degree of ionization [11].

Phenolic compounds are better studied; computational methods for studying the antiradical activity were also applied for other plant biologically active compounds. Vo et al. [35] investigated nine natural diterpenes by kinetic and thermodynamic calculations. It was revealed that the sequential proton loss electron transfer mechanism is favoured in polar solvents, whereas formal hydrogen transfer is the main pathway for the radical scavenging of these diterpenes in the gas phase and in lipid media. Vo et al. [36] also studied natural hydroxanthraquinones by kinetic and thermodynamic calculations. Computational methods were used to study the antiradical mechanisms of such plant compounds as products of the lignan family [37], kynurenines [38], coumarin-chalcone hybrids [39], essential oil components [40] etc.

Computational methods for studying the antiradical activity of plant compounds are based on the density functional theory and are used to calculate thermodynamic parameters associated with antiradical mechanisms (HAT, SET-PT and SPLET). BDE, IP, PDE, PA and ETE are the most informative thermodynamic parameters for evaluating the three main antiradical mechanisms. Thus, the results obtained by computational methods alone or in combination with experimental methods allow the thermodynamically advantageous antiradical mechanism for the studied compounds under specific conditions to be determined. However, it is worth noting that the determination of the mechanism of antioxidant action still does not allow prediction of the antioxidant mechanism of these compounds in organisms consisting of many complex individual systems.

5. Conclusions
Antioxidant potential of plant parts and their extracts, biologically active additives, food products, etc. should be considered as a combination of antioxidant and antiradical activities. This approach is not only more informative, but also more accurate. The existing experimental and computational methods and their combinations allow not only evaluation of the antioxidant potential, but also the study and suggestion of the antiradical mechanism of action of the target compounds. However, despite the broad methodological approaches discussed in this review, it is still impossible to determine the antioxidant mechanism of substances in vitro. Expensive and long-term experiments on cell cultures and animals are still required for antioxidant mechanism determination.
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