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A Tentative Classification of Antioxidants: Which Role They Play when Protecting Biological Targets from Oxidative Stress Induced Damage?

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Abstract

By studying the protection of oxidative stress induced damage in biomolecules by several groups of antioxidants, from the "side of the antioxidant", that is, by observing the reaction of the antioxidant itself with an oxidizing species and characterizing the resulting products, it was possible to classify the antioxidants into three different kinds. An antioxidant can act as a scavenger of the oxidizing species, repair a damaged biological molecule, or give new products with antioxidising activity, starting an antioxidising cascade. These three effects – scavenging, repair and cascade – can act in a separate or a cumulative way. This new classification of antioxidants by type of action can bring a new insight on the comprehension of the protection mechanisms and open perspectives to the design of new and more efficient antioxidants.

Keywords: Antioxidants; Scavenging; Repair; Cascade

Introduction

In the last decades a large amount of research work has been devoted to the study of antioxidants as protecting agents against oxidative stress induced damage on biological relevant molecules [1-3].

Oxidative stress can be defined as a biological consequence of chemical changes induced by oxidizing agents, namely the so called ROS (Reactive Oxygen Species) on molecules of living tissues. The ROS can be produced upon interaction of living matter with ionizing (gamma, beta or X rays) radiation or by exogenous agents, e.g. pollutants, xenobiotics or metabolites. Therefore, a large effort has been made to find molecules – the so called Antioxidants – that are able to protect biological targets from ROS induced damage, particularly from natural origin due to their importance as constituents of the regular human diet.

However, the huge amount of studies on protection of biological targets by antioxidants published so far, are almost entirely concerned on the protective effect of antioxidant against the damage of the biological target; that is, to observe how effective an antioxidant is on avoiding the oxidation of the biological molecule. Under this point of view, a good antioxidant is a molecule that preserves (total or partially) the biological molecule when submitted to oxidative stress conditions, due to the capacity of the antioxidant to scavenge oxidizing radicals, that can be measured by standard (test) methods [4-7].

Our research work on this field in the last two decades has been centered on the *other side*; which is to study what happens to the antioxidant itself when it reacts with a ROS [8-13]. Oxidizing radicals were produced by gamma radiolysis of appropriate aqueous solutions of the antioxidant and/or radiomimetic (photolytic or chemical) processes and the products were analyzed by chromatographic techniques (HPLC/GC-MS) [11-13]. In some cases, transient radicals were characterized by Electron Spin Resonance Spectroscopy [9,11,14].

The identification of the oxidation products of the antioxidant and (whenever possible) the intermediates involved can bring a new insight on the protection mechanism [9,11-13] and give hints to the design of new and more efficient antioxidants [15].

Types of Antioxidants

An antioxidant can be defined as *any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate* [16]. The reaction of an antioxidant with a ROS (e.g. an oxidizing radical) can occur by three different pathways:

sequential electron transfer - proton transfer (SETPT, controlled by the ionization potential/proton dissociation enthalpy); H atom abstraction (HAT, controlled by the bond dissociation enthalpy) and sequential proton loss - electron transfer (SPLET, controlled by the proton affinity/electron transfer enthalpy) [10]. No matter the reaction mechanism, the antioxidant is oxidized and produces a new radical that can behave differently when interacting with the biological target to be protected.

The scavenging effect

This is the most common effect, and the role it is expected an antioxidant to play to protect a biological target from oxidative stress induced damage. The general and classical studies concerning antioxidant capacities referred above are based on this effect. Considering that both the biological target (BT) and the antioxidant (AO) are present in a medium where oxidative stress conditions are produced, they both react with the damaging species (e.g. the oxidizing radical $OR^{\bullet}$), as illustrated in Scheme I.

$$BT + OR^{\bullet} \longrightarrow BT_{ox}^{\bullet} \quad (1)$$

$$AO + OR^{\bullet} \longrightarrow X^{\bullet} \quad (2)$$

Scheme I

The $X^{\bullet}$ radical formed in reaction (2) can now further react (or not) with the biological target. Whatever the case, considering that the oxidizing radicals are very reactive species (e.g. the hydroxyl radical, that reacts with organic and/or inorganic molecules with similar rate constants, close to the limit by diffusion) [13], Scheme I illustrates a phenomenon of simple and expected kinetic competition. If part of the oxidizing radicals is scavenged by the antioxidant, the biological target is consumed in a lesser extent. This has been observed e.g. on the protection of DNA bases by Xanthine derivatives [8].

The repair effect

From a chemical point of view, an antioxidant is a reducing species. In addition to the scavenging role referred to above, the antioxidant (AO) may also react by reducing the oxidized biological target ($BT_{ox}^{\bullet}$) back to the original form (BT), according to Scheme II.

$$BT + OR^{\bullet} \longrightarrow BT_{ox}^{\bullet} \quad (3)$$

$$AO + OR^{\bullet} \longrightarrow X^{\bullet} \quad (4)$$

$$BT_{ox}^{\bullet} + AO \longrightarrow BT + Y^{\bullet} \quad (5)$$

Scheme II

The repair effect illustrated by equation (5) of Scheme II was observed on a series of Xanthine derivatives, where oxidized forms of some Xanthines were reduced by other Xanthine derivatives, depending on the relative redox potentials of these compounds, as confirmed by cyclic voltammetry [9].

The cascade effect

More recent studies on Xanthine [12], Antipyrine [11] and Cinnamic Acid [13] derivatives have shown protective effects of antioxidants against oxidative stress induce damage on biological targets (e.g. the DNA base adenine) that cannot be attributed exclusively to the (combined) scavenging and repair effects discussed above. In those cases, some of the final stable oxidation products of the antioxidant (hence the importance of studying what happens after oxidation of the antioxidant itself) showed to be able to repair the oxidized biological target [11-13].

By using the hydroxyl radical as the ROS, some products resulting from hydroxylation of Xanthine derivatives (uric acid derivatives) or demethylation products showed to be able to repair radicals resulting from adenine oxidation [12]. In the case of antipyrine derivatives demethylation reactions from the amino group induced by the hydroxyl radical were also observed [11]. Finally, cinnamic acid and derivatives also demonstrated to give new and better antioxidants upon hydroxylation by the hydroxyl radical [13]. The overall and general situation is illustrated by Scheme III.

$$BT + OR^{\bullet} \longrightarrow BT_{ox}^{\bullet} \quad (6)$$

$$AO + OR^{\bullet} \longrightarrow X^{\bullet} \quad (7)$$

$$X^{\bullet} \longrightarrow \ldots \longrightarrow Pi, \ldots \quad (8)$$

$$OR^{\bullet} + Pi \longrightarrow W^{\bullet} \quad (9)$$

$$BT_{ox}^{\bullet} + Pi \longrightarrow BT + Z^{\bullet} \quad (10)$$

Scheme III

In Scheme III the competition between equations (6) and (7) illustrates the scavenging effect. The sum of equations (8) and (9) and/or (8) and (10) accounts for the cascade effect.

Conclusions

The examples presented in this short review enable the classification of the considered Antioxidants into three different types; concerning the role they play on the protection of biological targets against oxidative stress induce damage.

These tree kinds of action of antioxidants can occur in a cumulative way, e.g. scavenging effect plus repair effect, scavenging effect plus cascade effect or even all three effects together. This means, especially in the latter case, that one equivalent of an antioxidant can prevent several equivalents of a biological molecule to be damaged by an oxidizing agent.

However, the *in vitro* studies that enabled to draw these conclusions are not enough to establish the efficacy of a natural antioxidant or to appoint the design of new synthetic antioxidant. For example, a good antioxidant can yield a new product that can be either a prooxidant, an unreactive species or another (and even better) antioxidant. Regardless the case, the new product can have (or not) toxic properties, that must be

evaluated. Therefore, the chemical studies on antioxidants have always to be complemented by toxicological essays concerning safety for human health.

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