



Original Contribution

# Structure–property studies on the antioxidant activity of flavonoids present in diet

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## Abstract

The screening of natural flavonoids for their bioactivity as antioxidants is usually carried out by determination of their profile as chain-breaking antioxidants, by the evaluation of their direct free radical-scavenging activity as hydrogen- or electron-donating compounds. Since this may not be the only mechanism underlying the antioxidant activity it is important to check the ability of these compounds to act as chelators of transition metal ions. Accordingly, in the present study the acidity constants of catechin and taxifolin, as well as the formation constants of the corresponding copper (II) complexes, were investigated by potentiometry and/or spectrophotometry. Moreover, a detailed quantitative examination of the coordination species formed is presented. In addition, the partition coefficients of both catechin and taxifolin in a biomimetic system (micelles) were determined, since these properties may also contribute to the antioxidant behavior of this type of compound. The log *P* values determined depend on the electrostatic interactions of the compounds with the differently charged micelles (the highest values were obtained for zwitterionic and cationic micelles). The prooxidant behavior of the compounds was assessed through the oxidation of 2'-deoxyguanosine, induced by a Fenton reaction, catalyzed by copper. The data obtained reveal that the flavonoids under study did not present prooxidant activity, in this particular system. The results obtained are evidence of a clear difference among the *pK<sub>a</sub>*, the complexation properties, and the lipophilicity of the flavonoids studied, which can partially explain their distinct antioxidant activity. The most stable geometries of the free compounds were determined by theoretical (ab initio) methods, in order to properly account for the electron correlation effects which occur in these systems, thus allowing a better interpretation of the experimental data.

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## Introduction

Bioflavonoids are secondary phenolic plant metabolites distributed widely in nature and present in fruits, vegetables, and beverages. Apart from the purely academic study of their natural occurrence, distribution, biosynthesis, metabolism, and function in plants, flavonoids are becoming of increasing importance in applied science. Although a plethora of biological actions has been ascribed to this kind of compound, their antioxidant activity, in particular, has recently attracted much attention [1–5]. Numerous studies

*Abbreviations:* SPAR, structure–property–activity relationships; 2'-dG, 2'-deoxyguanosine; 8-OH-2'dG, 8-hydroxy-2'-deoxyguanosine; CTAB, cetyltrimethylammonium bromide; SDS, sodium dodecyl sulfate; HDPC, hexadecylphosphocholine; DFT, density functional theory.

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have been reported on dietary flavonoids, which are expected to have an important role in the prevention of coronary heart disease, cancer, and age-dependent neuropathologies [6–9]. Flavonoids are described as hydrogen-donating antioxidants by virtue of the reducing properties of the multiple hydroxyl groups attached to aromatic ring systems, along with their ability to delocalize the resulting phenoxyl radical within the structure. It is recognized that polyphenolic flavonoids are able to scavenge different reactive oxygen radicals, such as the hydroxyl and superoxide radicals [10–12].

Considerable attention has lately been focused on the role and mechanism of action of polyphenolic compounds, namely through their ability to chelate transition metals ions. Transition metals (especially iron and copper) are known catalysts of deleterious radical processes. Their reduced forms ( $\text{Fe}^{2+}$ ,  $\text{Cu}^+$ ) can promote the formation of hydroxyl radicals through the Fenton reaction, for example. Under normal conditions, transition metals almost do not exist freely in body fluids but are sequestered in proteins. However, in adverse circumstances this equilibrium can be broken, and the effect of antioxidant endogenous defenses and dietary polyphenols could be beneficial [13].

Copper, in particular, is a physiologically important redox-active metal that is known to be associated with endogenous oxidative damage, which likely involves the initial reduction of  $\text{Cu(II)}$  to  $\text{Cu(I)}$  by a variety of mechanisms [14].

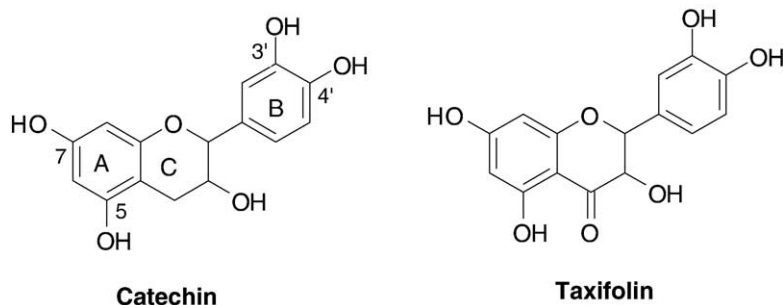
The antioxidant and/or antiradical activity of flavonoids has been studied in different model systems, although very few studies have been performed to date to gain an insight on the structure–property–activity relationships (SPAR). In fact, this may be a rather efficient approach for the design and development of new antioxidant agents and/or for the understanding of their mechanism of action. A structure–antioxidant–activity relationship of flavonoids (quercetin, rutin, kaempferol, and luteolin) has been proposed by Brown et al. [15]. A correlation was established between the structure of the flavonoids and their antioxidant activities with quercetin being the best antioxidant due mainly to the presence of a catechol group in ring B and a 3-hydroxy group in ring C. The lipophilicity of the com-

pounds was also evaluated and correlated with the antioxidant activity of the flavonoids.

Accordingly, the intrinsic properties of phenolic dietary antioxidants must be evaluated, in order to correlate these parameters with their activity or side effects (such as prooxidant activity) [16–20]. Antioxidants are often capable, according to their redox potential, of reducing transition metals and therefore allowing them to catalyze oxidative damage. This prooxidant activity happens mostly at low antioxidant concentrations.

Moreover some details on the mechanism of action of dietary compounds could be obtained which could allow the establishment of a suitable database for the discovery of the pharmacophore (or toxicophore) of this type of compounds.

The aim of the present study is to gain an insight into the antioxidant and/or prooxidant activity of structurally related phenolic compounds, such as the flavonoids present in the diet, mostly in grapes and wine, through the evaluation of their physicochemical properties. Given that flavonoids could compete for the complexation of transition metals with endogenous complexing agents and induce radical damage by generating a reduced form of the metal, and that their antioxidant properties are related to their lipophilicity/hydrophilicity according to the target system, it is important to quantify their complexation and partition capacities. Since information in this particular area of research is scarce and not fully understood, it is of the utmost importance to determine the physicochemical characteristics of phenolic compounds, mainly those that are intrinsically related to an oxidative behavior. Even though more than 4000 different flavonoids are found in nature [2], the present research is focused on two particular flavonoid structures, catechin and taxifolin, which belong to the subgroups of the flavanols and flavanones, respectively (Scheme 1). These specific flavonoids were chosen for their interesting structures, when compared to quercetin. They lack a 2,3-double bond isolating electronically the catechol group from the rest of the molecule. Therefore the influence of the catechol on the complexation toward copper can be assumed to be similar for both flavonoids. So, the results obtained can be ascribed to their only structural difference, the carbonyl group. The specific flavonoids were found in significant quantities (as monomeric species) in both fruits and wine, and taxifolin,



Scheme 1.

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