Biotechnology and Food Sciences

Review article

Flavonoids and their properties to form chelate complexes

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***Abstract**: The medical properties of naturally occurring compounds such as flavonoids have been well known for many years. However, the discovery that complexes of flavonoids with metal ions are more effective than free flavonoids changed the course of chemistry research. Flavonoids can be effective drugs because of their potent chelating or neuroprotective, radical scavenging and anti-inflammatory properties. Our paper is a literature review about flavonoids and their complexes which are generally used in medicine and pharmacy.*

***Keywords:** flavonoids; chelate properties, flavonoid complexes.*

Introduction

The processes of flavonoids chelation have been described by many authors. In this article we would like to present the information about reactions between different types of flavonoids and metal ions available in the literature.

Flavonoids are the wide group of compounds, which demonstrate the properties to form chelate complexes. In this review we present the chelation processes between flavonoids and metal ions. Flavonoids have specific chemical structure, which can undergo metal ion chelation process.

Flavonoids are benzopirone derivatives which are ubiquitous in nature. Over 4000 different flavonoids have been identified. The major sources of flavonoids are apples, red fruits, onions, citrus fruits, nuts and beverages such as tea, beer and wine. The basic structure of flavonoids is the flavylium cation (Fig. 1). Flavonoids are divided according to the chemical structure into several classes. Effects on flavonoids properties are related with their chemical structure and depends on it. Their antioxidant properties are related with hydroxyl group. Generally, the larger number of free hydroxyl groups corresponds with a greater scavenging effect, but their position in flavonoids skeleton is the crucial structural element.

Flavonoids, classification and characterization

Flavonoids are a group of polyphenolic compounds, diverse in chemical structure and characteristics, mainly found in fruits, vegetables and cereals.

Therefore, flavonoids are part of the human diet. Over 4000 different flavonoids have been identified within the major flavonoid classes which include flavonols, flavones, flavanones, catechins, anthocyanidins, isoflavones, dihydroflavonols, and chalcones. Flavonoids are potentially antioxidants, metal chelators and inhibit lipid peroxidation [1].

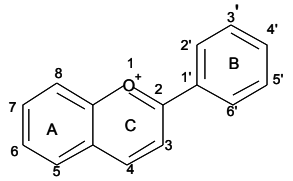

Figure 1. The structure of flavylium cation

Because of the polyphenolic nature of flavonoids can behave as antioxidants. These properties depend on the number of hydroxyl groups present on the flavonoid structure. It is said that if the number of hydroxyl groups in flavonoids is higher the antioxidant capacity is also better [2].

Flavonoids are divided into eight different groups: flavonols (quercetin, myricetin, kaempferol and rutin), flavanones (taxifolin), flavones (luteolin and apigenin), isoflavones (daidzein and genistein), catechins, anthocyanidins, dihydroflavonols and chalcones [3-4]. The carbon atoms in flavonoid molecules are assembled in two aromatic rings, commonly denoted as A and B, which are connected by a three-carbon "bridge": C_6–C_3–C_6 (Fig. 1.). Flavonoids are classified as flavanonols, flavonols, flavanones isoflavones or flavones (Fig. 2) [5].

Flavonoids are weak polybasic acids that are polyphenolic in nature and have a number of hydroxyl groups that can be subjected to protonation and deprotonation depending on their pK.

Flavonoids are important natural anti-oxidants. They have been extensively studied because of their numerous biological activity [6-9].

Nowadays many pharmaceuticals contain flavonoids as active substance. It is a proof that they are commercially available today. For example quercetin, the most biologically active and popular dietary flavonoid, is generally used as a dietary supplement [10].

Chelation process of flavonoids

Interactions of flavonoids with metal ions can lead to chelate formation. The chelation of metals can be crucial in the prevention of radical generation, which damage target biomolecules. Moreover, the using of natural chelators such as flavonoids, is better than the synthetic ones due their toxicity effects.

In the structure of several flavonoids are three potential coordination sites:

a) Between 5-hydroxy and 4-carbonyl group,
b) Between 3-hydroxy and 4-carbonyl group,
c) Between 3', 4'-hydroxy group in B ring (Fig. 3).

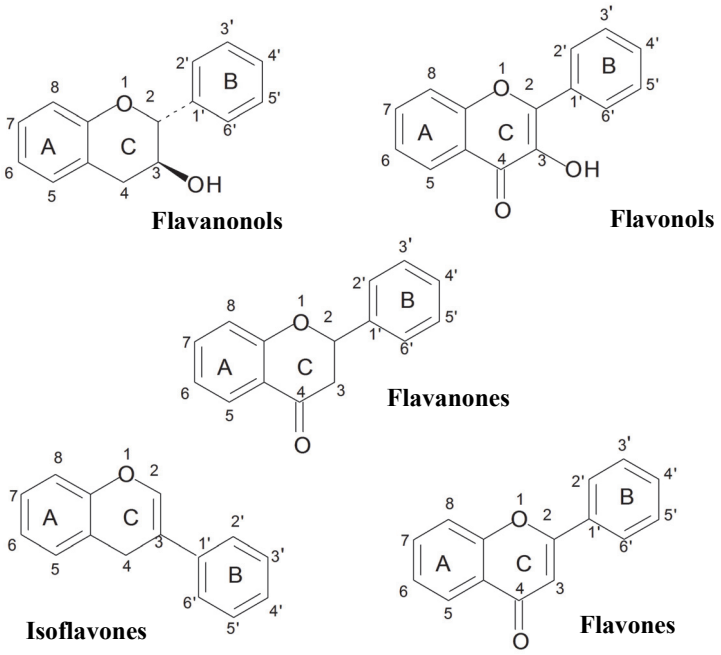

Figure 2. Structure of flavones

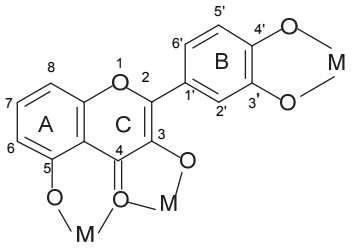

Figure 3. Potential coordination spaces in some structure of flavonoids [11]

These compounds can chelate many ion of metals and form different complexes. Metal-flavonoid complexes have a much stronger free radical scavenging properties than the free flavonoids. Moreover they play an important role in protection against oxidative stress. In order to determine their potential biological action, it has been extensive research on the physicochemical background. It was important to get to know something about their chemical structure. Many significant features were examined.

In 1962 the first complex of flavonoids with aluminum as the central ion was received. Since 1980, researchers have been studied over 40 metal complexes of flavonoids [12].

Due to the specific chemical structure, flavonoids can chelate metal ions and form complexes. In addition to direct free radical scavenging properties,

flavonoids have antioxidant activity thanks to interactions between the reduced forms of transition metals, mainly by iron and copper ions, which participate in the formation of free radicals. Flavonoids can chelate metal ions preventing them in the participation to form free radicals, and protect against oxidative stress. Thus, the overall antioxidant flavonoids seems to be a combination of direct reaction with free radicals and chelating properties responsible for the production of reactive oxygen species.

Many studies have confirmed that flavonoids can behave as antioxidants because of their chelating properties. Furthermore, experimental data show that the chelates are much more effective in scavenge free radicals than the free flavonoids. *Kostyuk* et al. [13] found that complexes of rutin and epicatechin with iron(II), iron(III), copper(II) and zinc(II) are more effective in free radicals scavenging than the free flavonoids. These complexes show increased efficiency in the protection of red blood cells against asbestos, which causes oxidative damage *in vitro*. By the same authors the copper complex rutin is recognized as the most effective antioxidant against asbestos, causing lipid peroxidation in lung tissue *in vivo*. *Moridani* et al. [14] found that flavonoid complexes of iron(III) are much more effective than the free flavonoids in protection of hepatocytes against hypoxia in laboratory rats. Using a synthetic free radical, 1,1-diphenyl-2-picrylohydrazyl, *de Souza* et al. and *Bravo* et al. [15,16] found that the antioxidant properties of quercetin, rutin, catechin and galangin complexes are more effective than the free flavonoids. Quercetin is a potential antioxidant and the main flavonoid among flavonols. The biological activity of quercetin affects the presence of metal ions. Hydroxyl groups present in the structure of quercetin are capable of forming complexes with various ion of metals. Quercetin chelates metal ions *via* 3' or and 4' phenolic group. *Bukhari* et al. and *Zhou* et al. [17,18] found that the antioxidant activity of flavonoids depends on the number and position of hydroxyl groups in the flavonoid structure. Copper(II)-quercetin complex has higher antioxidant activity than free quercetin. The same results were obtained for cobalt(II)-quercetin and aluminum(III)-quercetin complexes. The complexes of quercetin with trivalent rare metals can bind to the DNA thereby changing its transcription, thus inhibiting growth of cancer cells. *Brown* et al. [19] found that quercetin and rutin have a greater ability to delay the oxidation process by reacting with the copper(II) ion. Comparison of flavonoids in the prooxidant processes emphasizes the connections between free radical scavenging and metal chelation. *Afanas'ev* et al. [20] found that complexes of rutin with iron(II) and copper(II) are more efficient in free radicals scavenging than free rutin *in vitro* and *ex vivo* experiments. *Mira* et al. [21] found that only miricetin and quercetin effectively reduce iron(III). Rutin, catechin and taxifolin are moderately active, while kaempferol and luteolin are relatively weak regulators.

Morin (3,5,7,2',4'-pentahydroxyflavon) complexes with Cu(II), Pt(II), La(III) and Gd(III) showed greater antioxidant activity and free radical scavenging than

free morin. Due to the antioxidant mechanism, morin complexes showed an inhibition behavior against three strains of bacteria such as *Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus* [22].

Chen et al. [23] found the chelate complexes of biochanin A-(4'-methoxy-5,7-dihydroxy-isoflavone) with copper(II) and nickel(II) ions. These complexes demonstrate the antiviral , anti-cancer and antioxidant activity. *Jurd et al.* [12] reported that in the case of isoflavones, the most probable sites of the metal chelation are 4-carbonyl and 5-hydroxy groups. *Dowling* et al. [24] showed that copper isoflavone chelates have higher antioxidant activity than free isoflavones while the iron isoflavone chelates showed pro-oxidant activity compared to the free isoflavone. Moreover, the copper naringenin complex has a higher anti-inflammatory and antioxidant activity than free naringenin. The increase in biological activity of the complex may be related to the specific coordination environment in naringenin molecule [25].

It is generally accepted that the ability of flavonoids to chelate metals is very important for their antioxidant activity.

Complexes of flavonoids have the impact on the reduction of toxic metals bioavailability. For example, the overload of aluminum leads to neurological disorders. Quercetin complex with aluminum(III) reduces the excess aluminum in diet. Therefore, they seem to be an appropriate antidote in heavy metal poisoning *in vivo*. Quercetin as a biologically active ligand, can be a suitable chelator for molybdenum(VI). Its complex could be used in the case of molybdenum deficiency instead of molybdenum salts which cause toxic effects. [26, 27].

This review clearly shows that the interactions of flavonoids with metal ions, can play important role in human body and prevent against many disorders.

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