



Hydroxyflavone metal complexes - molecular structure, antioxidant activity and biological effects



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ABSTRACT

High content of hydroxyflavones in fruits, vegetables, cereals and herbs makes them a common component of the human diet. Because of their antioxidant, antiviral, antibacterial, anti-inflammatory, anticancer properties they still pay an attention of many scientific centers. Hydroxyflavones may form complexes with metal cations, and their chelating properties differ significantly depending on the number and position of hydroxyl substituents in the ring. Synthesis of new complexes of hydroxyflavones allows for improvement biological properties, stability, water-solubility, hydrophilicity, bioavailability comparing with the parent hydroxyflavones. It expands the applicability of hydroxyflavones as food additives, diet supplements, preservatives or drug. This paper reviews on the procedures of synthesis of metal complexes with hydroxyflavones, their molecular structure, mode of coordinations, spectroscopic properties and their biological activity. The dependency between the biological activity of these compounds and their molecular structure is discussed.

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1. Introduction

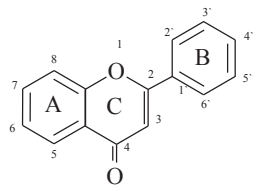
Flavones belong to the large group of secondary plant metabolites called flavonoids. The basic skeleton of flavones is constituted of 2-phenyl-1-benzopyran-4-one moiety, i.e. two benzene rings (A

and B, one with the C2=C3 double bond) connected to each other by an oxygenated heterocycle ring C (scheme Table 1). In plant tissues they are present rather as coupled with sugars or simple acids and not as aglycones. Flavones play an important role in the defense of plants against microorganisms (bacteria, fungi, viruses), against herbivores and other competing plants (allelopathic properties) [1–4]. On the other hand, they are flavones which attract animal for pollination and seed dispersal purposes. Moreover some of flavonoids show important metabolic properties during nitrogen

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Table 1
The skeleton structure of selected flavones with hydroxyl groups.



Ring	A				B		
	5	6	7	8	2'	3'	4'
Primuletin	OH						
Chrysin	OH						
7,8-dihydroxyflavone			OH	OH			
3',4'-dihydroxyflavone						OH	OH
Apigenin	OH			OH			OH
Baicalein	OH	OH		OH			
Baicalin	OH	OH		OR			
Luteolin	OH			OH		OH	OH

R = glucuronic acid.

transport or storage and they are UV protectors. A lot of flavones have been identified in plants so far, some of them are listed in Table 1. They are mainly found in cereals (millet, wheat) [5], herbs [6], mostly from *Lamiaceae*, *Asteraceae* and *Apiaceae* families [4] (e.g. *Ginkgo* and Chinese medicinal plants *biloba* [7] and *Oroxylum indicum* [8]), mainly in flowers and leaves of plants. Many health benefits are connected with high consumption of flavone-rich foods including reduced risk for heart diseases, cancer, neurodegenerative psychic diseases, and many other chronic diseases. It is assumed that oxidative stress play an important role in the genesis of these diseases, and therefore flavones may possess therapeutic effects through antioxidant mechanisms. In addition to their antioxidant properties, flavones exhibit other multiple biological effects, i.e. antibacterial, antiviral, anti-inflammatory, anticarcinogenic, anti-ischemic, hypolipidemic, antimutagenic and many others [9–16].

Much attention is paying to new metal complexes of hydroxy-substituted flavones because they possess different physico-chemical and biological properties than the ligand alone [17–23]. Among others, the antioxidant activity of some metal complexes with flavones was higher than the parent flavones. It was reported that metal ions in flavone-complex may act as radical scavenging center or may act as a Fenton catalyst whereas ligand moiety is a target for hydroxyl radical and therefore the antioxidant activity of metal complex is higher than the flavone [24]. The type of metal coordination is crucial for the antioxidant properties of metal complexes with flavones. The main coordination sites in the structure of 5-hydroxy substituted flavones are 5-hydroxy (in A ring) and 4-carbonyl (in C ring) groups. For example copper (II) may be chelated by primuletin [17], chrysin [18] and apigenin [19] involving O4/O5 coordination sites. However hydroxyl groups substituted in *ortho* position in ligand molecule can also take part in metal ion chelation, for example: 3'- and 4'-hydroxyl groups in B ring (3',4'-dihydroxyflavone and luteolin) or 6,7- (baicalein) and 7, 8- (7,8-dihydroxyflavone) catechol groups in A ring. Riha et al. [20] studied interactions of 26 flavonoids with Cu(II) as well as Cu(I) ions and found that the most efficient copper chelation sites in flavones were O4/O5, O5/O6 or O6/O7. The ability to chelate metals was increasing with the number of free hydroxyl groups in the ring A in flavone molecules, but it was clearly less effective than coordination *via* 3-hydroxyflavone (flavonol).

Because of poor water solubility and bioavailability of flavonoids, their use in food industry or pharmacy is limited. However,

the formation of metal complexes may increase solubility, hydrophilicity and bioavailability of flavonoids and therefore enlarge the area of new application.

There are several reviews that concern the metal complexes of flavonoids, but they mainly describe the biological properties [25–28]. In this work we focused on metal complexes with flavones possessing hydroxyl groups in different positions in the rings. The methods of synthesis as well as the molecular structure and types of metal coordination are extensively described. The dependency between structure of metal complexes with hydroxyflavones and their biological activities are discussed. Therefore the presented work brings new information in the field of potent application of novel formulation of hydroxyflavone derivatives as food additives, supplements, preservatives or drugs.

2. Molecular structures of flavone metal-complexes

X-ray diffraction of monocrystal in the best way describes the structure of synthesized complexes in the solid state. Unfortunately, there are often difficulties associated with the preparation of the single crystal of metal complexes with flavones [21]. On the other hand there was no literature data on the crystal structure of metal complexes with flavonoids that have more than one possible metal binding site [22]. For this reason, there are few reports describing the crystallographic structure of flavonoids complexes with metals. Single crystals of Fe(III)-3-hydroxyflavone complex suitable for X-ray diffraction were obtained by Amrani et al. [23]. [Fe(3HF)₂Cl(MeOH)] complex was detected as monomeric with a solvent molecule in the coordination sphere and pseudo octahedral coordination geometry around the metal ion. X-ray structure of [Cu(II) (3HF)₂] complex was defined as square-planar geometry [25], 3-hydroxyflavone, however, belongs to flavonols. As regard to flavone complexes with metals, according to our knowledge there is no X-ray structure in crystallographic base.

In literature one could find many reports particularly describing the procedures of preparation of flavone metal complexes in solid state [17–19,29–33]. The main steps of syntheses of several selected compounds are gathered in Table 2. A review of the literature shows that methanolic or ethanolic solutions of ligands were mainly used to obtain metal complexes. Metal salt (mainly chloride, sulfate or acetate) was usually added in appropriate molar ratio either in solid form or as the solution in methanol, ethanol or water to flavone (mostly alcoholic) solution. The reaction mixture were usually adjusted to pH 6–8 in room temperature. In the case of aluminum complex with luteolin product precipitated after 5 days. Sometimes the continuous stirring was carried out to precipitate metal hydroxyflavone complexes. In other cases, mixtures were refluxed to obtain solid product (1–3 h for primuletin complexes, 12 h for apigenin-cooper complex but in the case of lanthanide-luteolin complexes only 30 min reflux was required). Obtained products were filtered and washed mainly with ethanol or methanol and then dried in vacuum, air or in desiccators over calcium chloride.

The composition of synthesized complexes was determined predominantly using C, H, N elemental and thermogravimetric analysis. For example molecular formulas of primuletin complexes with zinc and magnesium cations were determined as [Zn₂(Prim)₂SO₄(H₂O)₆]·2H₂O [17] and [Mg(Prim)₂(H₂O)₂]·H₂O [30].

The aim of our review is biological activity of metal flavone complexes, thus the composition of solutions of titled compounds are interesting for us. Most of the complexes were examined in water, ethanol, methanol or water/alcohol solutions (Table 3). However some studies were carried out in conditions similar to physiological (e.g. baicalein-Fe²⁺/Fe³⁺ in phosphate buffer). The

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