Chapter 14

Flavonoid Complexes as Promising Anticancer Metallodrugs

Valentina Uivarosi and
Alexandra-Cristina Munteanu

Additional information is available at the end of the chapter

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Abstract

Flavonoid metal complexes commonly exhibit an improvement of biological activity compared to the parent ligands. This chapter is focused on the antioxidant and anticancer properties of flavonoid metal complexes, in correlation with their binding ability to vital macromolecules such as nucleic acids and serum proteins. Perspectives for an adequate formulation of these complexes were also discussed.

Keywords: flavonoids, metal complexes, anticancer properties, nucleic acid binding, protein binding, formulation

1. Introduction

The urgency to overcome the biophysical and biomedical drawbacks of current chemotherapeutic treatments led the scientists to consider flavonoid metal complexes as viable options in cancer therapy. Both *in vitro* and *in vivo* studies report that flavonoids and their metal ion complexes exert pleiotropic effects on tumor promotion and progression.

Our work is an attempt to help the design of novel flavonoid-metal ion complexes with improved pharmacological activity and a broader range of antitumor mechanisms of action. In this chapter, we have analyzed relevant data available in literature on the antitumor activity of the flavonoid-metal ion complexes, regarding their cellular targets, their role in cancer cell death, growth and proliferation, and structure-activity analysis.

A novel metal-based compound with antitumor activity and promising clinical efficacy should meet the following criteria: (1) possess good intrinsic properties, molecular stability, allowing

the drug to arrive intact at the target cells; (2) exert efficient interaction with transport proteins in blood and membranes; (3) show good DNA-binding properties; (4) have selective activity against cancerous cells over normal cells; and (5) preferably have activity against tumor cells that are resistant to cisplatin and derivatives. These aspects will be discussed in the following pages.

2. Flavonoids: general information, main classes, and chelating properties

Flavonoids (from the Latin "flavus," yellow) are secondary plant metabolites naturally occurring in seeds, fruit skin, peel, and bark of plants [1]. Flavonoids are important components of the human diet, the major sources of flavonoids being apples, red fruits, onions, citrus fruits, nuts, and beverages such as tea, beer, and wine [2]. Although they are not considered nutrients, due to the variety of pharmacological activities in the mammalian body, flavonoids are more correctly referred to as "nutraceuticals" [3].

These compounds possess a common flavane (2-phenyl-benzo-γ-piran) nucleus, consisting of an aromatic A-ring fused to a heterocyclic C-ring, attached through a single carbon-carbon bond to a benzene B-ring (**Figure 1**).

According to the oxidation degree of the C-ring, the hydroxylation pattern of the nucleus, and the C^3 substituent, the flavonoids can be categorized into seven subclasses: flavones, flavonols, flavanones, flavanols (catechins), flavanonols, isoflavones, anthocyanins, and anthocyanidins [4–6]. Thus, the total number of polyphenolic compounds exceeds 4000. In all these subclasses, rings B and C are linked at C^2, with the sole exception of the isoflavones (linked at C^3). Many flavonoids occur naturally as glycosides; the carbohydrate substituents include D-glucose, L-rhamnose, glucorhamnose, galactose, and arabinose [7]. **Table 1** lists the subclasses of flavonoids, and a set of representatives, to which we will refer to in this chapter.

Flavonoids possess three possible metal-chelating sites that can bind metal ions: (i) the 3-hydroxy-4-ketone groups in the C-ring, (ii) the 5-hydroxy group in the A-ring and 4-carbonyl group in the C–ring, and (iii) 3′,4′-dihydroxy groups, located on the B-ring (**Figure 2**).

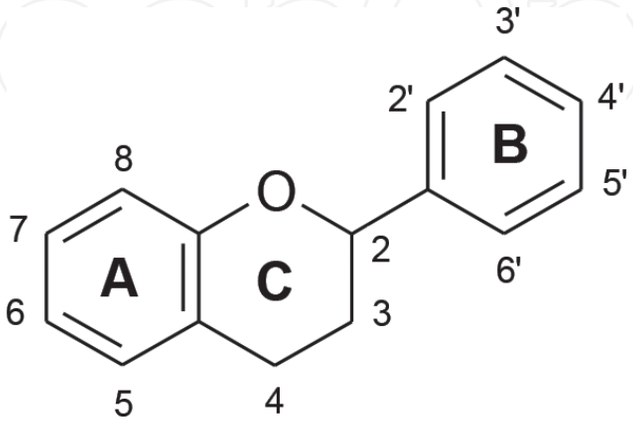

Figure 1. Basic flavonoid structure.

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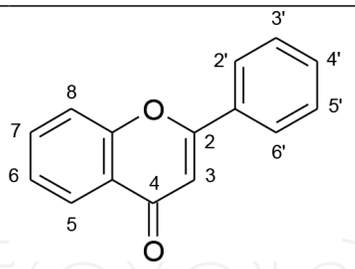
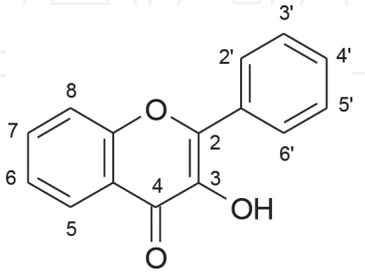
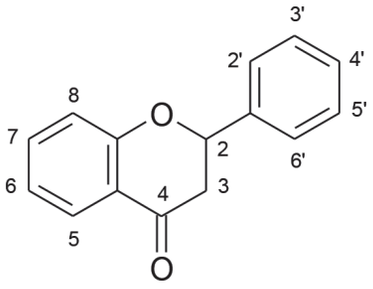
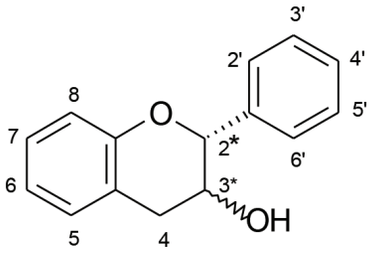
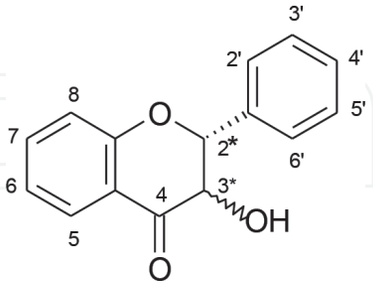
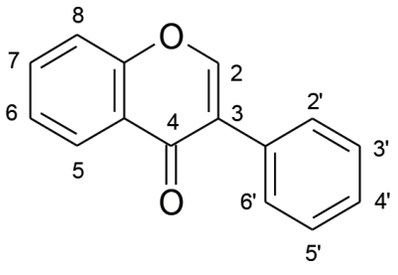
Flavonoid subclass	General structure	Representatives
Flavones		Chrysin: 5=7=OH Apigenin: 5=7=4′=OH Luteolin: 5=7=3′=4′=OH Diosmetin: 5=7=3′=OH, 4′=OCH_3 Diosmin: Diosmetin-7-rutinoside
Flavonols		Fisetin:7=3′=4′=OH Kaempferol: 5=7=4′=OH Quercetin: 5=7=3′=4′=OH Morin: 5=7=2′=4′=OH Myricetin: 5=7=3′=4′=5′=OH Galangin: 3=5=7=OH Rutin: Quercetin-3-rutinoside
Flavanones		Naringenin: 5=7=4′=OH Hesperetin : 5=7=3′=OH, 4′=OCH3 Naringin: Naringenin-7-neohesperidoside Hesperidin: Hesperitin-7-rutinoside Dio
Flavanols		Catechin (2*R, 3*S): 5=7=3′=4′=OH Epicatechin (2*R, 3*R): 5=7=3′=4′=OH Epigallocatechin (2*R, 3*R): 5=7=3′=4′=5′=OH Epicatechin gallate (2*R, 3*R): 5=7=3′=4′=OH, 3-gallic acid ester Epigallocatechin gallate (2*R, 3*R): 5=7=3′=4′=5′=OH, 3-gallic acid ester
Flavanonols		Taxifolin (2*R, 3*R): 5=7=3′=4′=OH
Isoflavones		Daidzein : 7=4′=OH Genistein: 5=7=4′=OH

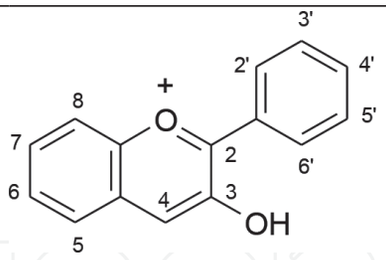
Flavonoid subclass	General structure	Representatives
Anthocyanidins, anthocyanins		**Anthocyanidins** Pelargonidin: 5=7=4′=OH Cyanidin: 5=7=3′=4′=OH Delphinidin: 5=7=3′=4′=5′=OH Malvidin: 5=7=4′=OH, 3′=5′=OCH **Anthocyanins** Cyanidin 3-glucoside Cyanidin 3-galactoside Cyanidin 3-rutinoside Malvidin 3-glucoside

Table 1. Main flavonoid [21] subclasses.

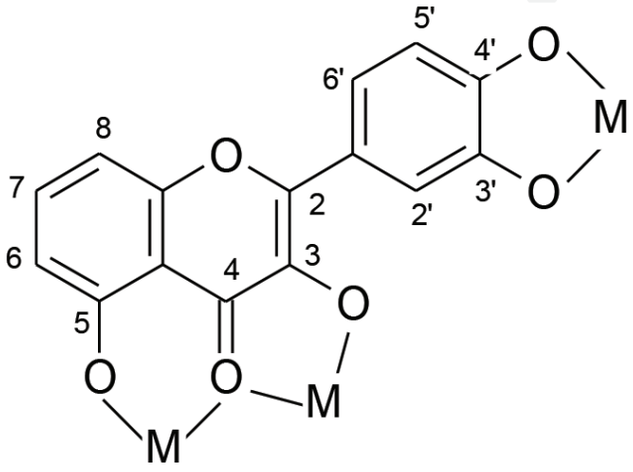


Figure 2. Typical chelation sites in forming the flavonoid complexes [2].

Cornard and Merlin [8] have reported that in acidic conditions, the 3-hydroxy-4-ketone or the 5-hydroxy-4-keto groups of quercetin (Q) are involved in coordination, whereas in alkaline milieu, the second chelating site, 3′,4′-dihydroxy group, located on the B-ring, is also involved.

3. Antioxidant and prooxidant activity of flavonoids and their metal complexes

Flavonoids have been reported to possess various biological effects: anticarcinogenic [9–11], antiviral [12], anti-inflammatory, immune stimulation [13, 14], antiallergic [15], and reducing the risk of cardiovascular disease [16–18].

Many of these beneficial health effects, including anticancer activity, arise from the antioxidant properties of these polyphenolic compounds [19], which are based on the following mechanisms:

(1) Direct radical scavenging: the flavonoid molecules are oxidized by free radicals (R•) resulting in more stable, less reactive radicals [20]:

$$\mathrm{FlOH} + \mathrm{R}\bullet \rightarrow \mathrm{FlO}\bullet + \mathrm{RH} \quad (1)$$

where R• refers to either reactive oxygen species, ROS (hydroxyl, superoxide, peroxyl, alkyl peroxyl), or reactive nitrogen species, RNS (nitric oxide, peroxynitrite).

(2) Chelation of metal ions; the property of flavonoids to form chelates can be considered from two points of view:

- flavonoids bind metal ions like Fe(II), Fe(III), and Cu(II), thus preventing free radical generation in Fenton reactions:

$$M^{n+} + H_2O_2 \rightarrow M^{(n+1)+} + OH^- + OH\bullet \quad (2)$$

- flavonoids form metal complexes that are generally more powerful antioxidants than the free ligands.

(3) Inhibition of various enzymes that are responsible for ROS/RNS formation (xanthine oxidase, reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase).

(4) Upregulation of enzymatic and non-enzymatic systems involved in the elimination and detoxification processes of oxidant species, such as reduced glutathione (GSH), GSH peroxidase, superoxide dismutase, and so on.

(5) Regeneration of the antioxidant species such as ascorbate and α-tocopherol by electron transfer reactions [5].

Many studies have correlated the antioxidant activity of flavonoids with the following structural features (**Figure 3**):

1. *ortho*-dihydroxy substitution in the ring B;

2. the presence of a 2,3 double bond and of a 4-oxo function;

3. a 3-hydroxy-4-keto and/or 5-hydroxy-4-keto conformation [21].

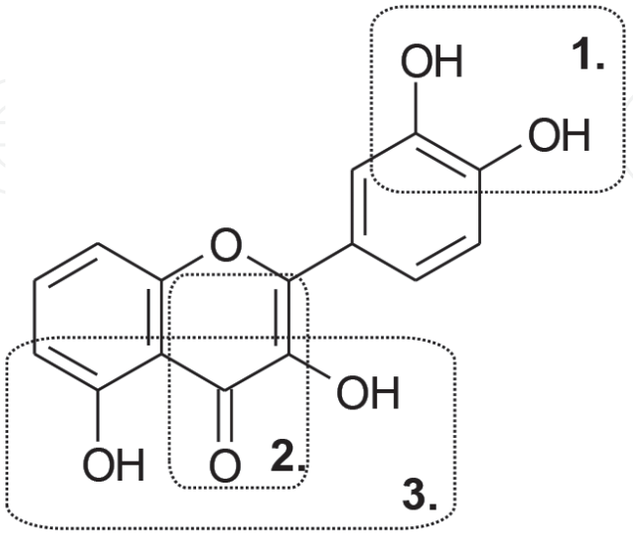


Figure 3. Main structural features required for antioxidant activity of flavonoids.

Among these main structural properties, it was observed that the antioxidant activity increases with the number of hydroxyl substituents and that the aglycones are more potent antioxidants than their corresponding glycosides [22].

Apart from the antioxidant activity, flavonoids can also exhibit prooxidant activity. This behavior is associated with the low one-electron reduction potentials; some of them may autoxidize slowly under neutral conditions and faster in alkaline media, generating ROS [23]. Another mechanism of prooxidant activity is correlated with their ability to reduce Cu^{2+} and Fe^{3+}, thus generating Fe^{2+} and Cu^{+} which in turn reduces hydrogen peroxide to hydroxyl radicals [24]. Prooxidant activity is thought to be directly proportional to the total number of hydroxyl groups [25], especially in the B-ring [26], and the concentration of the flavonoid [27].

Commonly, the prooxidant activity of flavonoids has been associated with various toxic effects, but it is also possible for it to generate beneficial properties. For example, the apoptotic and bactericidal activity of epigallocatechin gallate is based on its ability to reduce O_2 to yield H_2O_2 [28]. Likewise, the capacity of flavonoids to stimulate the activity of the detoxifying enzymes is a major mechanism for the chemopreventive properties of flavonoids, thus protecting the organism against mutagens and carcinogens [29].

A great number of metal complexes of flavonoid derivatives have been obtained, in order to improve the antioxidant activity of the parent flavonoid (**Table 2**).

Complex	Molar ratio metaion:ligand	Effect on the flavonoid antioxidant activity	Ref.
Flavonoid subclass: flavones			
VO(II)-luteolin	1:2	Increase	[30]
Ge(IV)-chrysin	1:1	Increase	[31]
VO(II)-chrysin	1:2	Increase	[32], [33]
Ce(IV)-chrysin	1:2	Increase	[34]
VO(II)-diosmin	1:1	Increase the scavenging activity only for $ROO^{\bullet}$, not for $O_2^{\bullet-}$, $DPHH^{\bullet}$, $OH^{\bullet}$	[35]
Flavonoid subclass: flavonols			
Mg(II)-quercetin	1:1	Increase	[36]
Al(III)-quercetin	2:1	Increase	[37]
Ge(IV)-quercetin	2:1	?	[38]
Sn(II)-quercetin	Not determined	Slightly decrease	[39]
Fe(II)-quercetin	1:2	Increase	[40]
Co(II)-quercetin	2:1	Increase	[41]
Cu(II)-quercetin	1:1	Increase	[42]
Cu(II)-quercetin	2:1	Increase	[43]
Cd(II)-quercetin	1:1	Decrease	[44]

Complex	Molar ratio metaion:ligand	Effect on the flavonoid antioxidant activity	Ref.
M(II)-quercetin M = Mn, Co, Ni, Cu, Zn	1:2	Increase	[45]
M(II)/(III)-quercetin M(II) = Fe, Cu, Zn M(III) = Al	2:1	Increase	[46]
Ln(III)-quercetin Ln = La, Nd, Eu, Gd, Tb, Dy, Tm, Y	1:3	Increase	[47]
VO(II)-morin	1:2	Increase the scavenging activity for $OH^{\bullet}$ and O_2^{-} Decrease scavenging activity for $ROO^{\bullet}$.	[48]
Cr(III)-morin	1:2	Increase	[49]
Cu(II)-morin	1:1	Increase	[50]
M(II)/(III)-galangin M(II) = Fe, Cu, Zn M(III) = Al	1:1	Increase	[46]
Sn(II)-rutin	1:2	Decrease	[51]
Sn(II)-rutin	3:2	Decrease	[52]
Cr(III)-rutin	2:1	Slightly increase	[53]
Cr(III)-rutin	3:1	Increase	[54]
VO(II)-rutin	1:2	Increase	[55]
Ni(II)-rutin	1:2	Increase	[56]
Cu(II)-rutin	1:1	Increase	[57]
Zn(II)-rutin	2:1	Increase	[58]
Flavonoid subclass: flavanones			
Cu(II)-naringenin-phenanthroline	1:1:1	Increase	[59]
M(II)-naringenin M=Cu, Zn, Ni	1:2	Increase	[60]
Ce(IV)-naringenin	1:2	Increase	[34]
Cu(II)-hesperetin-phenanthroline	1:1:1	Increase	[59]
Cu(II)-naringin	1:1	Increase	[61]
VO(II)-hesperidin	1:1	Increase	[62]
Flavonoid subclass: flavanols			
M(II)/(III)-catechin M(II) = Fe, Cu, Zn M(III) = Al	1:1	Increase	[46]
Al(III)-catechin	1:1	Decrease	[37]
Flavonoid subclass: isoflavones			
Cu(II)-genistein Fe(III)-genistein Cu(II)-biochanin A Fe(III)-biochanin A	1:2	Increase for Cu(II) Prooxidant activity for Fe(III)	[63]
Ce(IV)-daidzein	2:1	Increase	[34]

Table 2. Metal complexes of flavonoids investigated for their antioxidant activity.

By analyzing the data from **Table 2** and the scientific literature, some observations appear to be relevant:

- most metal complexes behave as more powerful antioxidants compared to the parent flavonoids;
- the higher antioxidant activity of the metal complexes was generally explained by acquisition of an additional radical-scavenging metal center by the complexes, probably a superoxide-dismutase-mimicking center;
- in some cases, the metal (e.g., Sn^{2+}, Cd^{2+}) complexes show lower antioxidant activity than the parent flavonoids; the lower antioxidant activity can be explained by the fact that chelation of these metal ions significantly changes the chemical properties of the flavonoid, or might increase the oxidation potentials relative to those of the free flavonoid;
- some metal complexes, especially those of Fe(III) ions, display prooxidant activity.

4. Anticancer activity of flavonoids metal complexes

The cytotoxic activity of flavonoids involves the inhibition of several molecular targets and pathways: DNA topoisomerases I and II [64], cyclin-dependent kinases CDK2 and/or CDK1 [65], androgen receptor signaling [66], actin polymerization [67, 68], activation of p53, and inhibition of NFkB pathways [69]. Flavonoids activate the caspase-mediated signal transduction pathways, consecutively stimulating the tumor-suppressor protein p53, which consequently triggers cell apoptosis [69].

In many cases, the antitumor activity of the flavonoid metal complexes has been reported to be greater than that of the free corresponding flavonoids [47]. This may be mediated through the regulation of important cell-cycle events, alterations in the DNA structure, prooxidant effects, or interactions with the phospholipid bilayer. Flavonoid metal complexes have been reported to be active against gastric cancer cells, human hepatocellular carcinoma cells [70], human cervical carcinoma cells [71], leukemia cells [61], human colon adenocarcinoma cells, human hepatoma cells, and osteoblast cancer cells [62]. A very important and promising feature displayed by these complexes is that a number of them have proven to be selective toward cancerous cells over normal cells [72]. **Table 3** contains a selection of metal complexes of flavonoids which have shown antitumoral activity.

As it has been shown in **Table 5**, complexes contain diverse structures, derived from the variety of flavonoids and metal ions used in the drug design. Regarding the flavonoid structures in metal complexes, the type of the substituents on either ring in the ligand structure, whether electron-withdrawing or electron donating, seems to have minor importance. However, their position appears to be crucial for the cytotoxic activity. *Ortho*-substitution of the B-ring appears to be unfavorable, while *meta*- and *para*-substitution augments the anticancer activity. This may be due to a structural effect, as the B (phenyl)-ring is more twisted in the *ortho*-substituted compounds than in the *meta*- and *para*-derivatives, which may increase the interaction with biological targets. The purpose of combining these ligands with metal centers is to obtain anticancer agents with extended mechanistic range, facilitating single-molecule multi-target anticancer therapy.

Complex	Comments	Ref.
4′-Methoxy-5,7-dihydroxy-isoflavone Complexes with Mn(II)*, Cu(II), Zn(II), Co(II), Ni(II) Metal ion:isoflavone molar ratio 1:2	Cell lines: *HeLa* (cervical cancer), *MDA-MB-435* (breast carcinoma), *SW620* (colon carcinoma), *HepG2* (liver cancer), *A549* (non-small-cell lung carcinoma). *was most efficient, especially on line SW620 (IC_{50} < cisplatin). Flow cytometry analysis showed that * acts in the G2/M phase of the cell cycle, causing early apoptosis.	[73]
Rutin complex with Zn(II) (Znrut) Metal ion:isoflavone molar ratio 1:1	*KG1* (leukemia): IC_{50} = 91.4 μM; *K562* (leukemia): IC_{50} = 173.2 μM; *Jurkat* (leukemia): IC_{50} = 150.2 μM; *RPMI8226* (multiple myeloma): IC_{50} = 196.6 μM; *B16F10* (melanoma): IC_{50} = 160.7 μM; *SK-Mel-28* (melanoma): IC_{50} = 194.0 μM. In the Ehrlich ascites carcinoma model, Znrut exerts modulating effect of mitochondrial membrane potential and expression of genes involved in cell cycle control, apoptosis and angiogenesis.	[74]
Diosmin complex with oxovanadyl (IV) [VO(dios)$(OH)_3$]$Na_{5.}6H_2O$ (VOdios)	*A549*: dios- IC_{50} > 100 μM, at 100 μM, VOdios decreases cell viability by 31%; *T47D* (breast tumor): dios exerts no antiproliferative effect, VOdios – IC_{50} = 23.3 μM; *SKBR3* (breast adenocarcinoma): dios – IC_{50} > 100 μM, VOdios – IC_{50} = 46.4 μM; *MDAMB231* (breast adenocarcinoma): dios – IC_{50} = 70 μM, VOdios – IC_{50} = 11.6 μM. An antiproliferative non-apoptotic mechanism, caspase 3/7 and oxidative stress independent, has been proposed.	[35]
Luteolin complex with oxovanadyl (IV) [VO(lut)$(H_2O)_2$]Na·$3H_2O$ (VOlut)	*MDAMB231*: IC_{50} = 17 μM (lut: IC_{50} = 88.3 μM); *A549*: IC_{50} = 60.5 μM (lut: IC_{50} = 66.3 μM); Both Lut and VOlut generate ROS and mitotic arrest; VOlute causes nuclear and cytoplasmic membrane damage.	[75]
Naringenin complex with oxovanadyl (IV) [VO$(nar)_2$]·$2H_2O$ (VOnar)	*A549*: nar shows no antiproliferative effect, VOnar: IC_{50} > 100 μM (at 100-μM cell viability decreases by 35%); *SKBR3*: nar shows no antiproliferative effect, VOnar: IC_{50} = 73 μM; *MDAMB231*: nar: IC_{50} > 100 μM (at 100-μM cell viability decreases by 30%), VOnar: IC_{50} = 20 μM. VOnar antiproliferative effect was accompanied by ROS generation, cell membrane damage and DNA degradation, cell cycle arrest, caspase 3/7 activation, and mitochondrial membrane potential decrease.	[76]
Chrysin complex with oxovanadyl (IV) [VO$(chrys)_2$EtOH]$_2$ (VOchrys)	*MC3T3E1* (normal osteoblast cell line), *UMR106* (osteosarcoma). Both the ligand and the complex exert similar inhibitory effect on normal cells and cancer cells (60% inhibition at 100 μM for osteosarcoma cells). Complexation does not improve the antitumor properties of the free flavonoid. *In vitro* and *in vivo* studies were performed on 3D human osteosarcoma and xenograft osteosarcoma mice models. The pharmacological results show that VOchrys had an inhibitory effect on cell viability, affecting the shape and volume of the spheroids and suppressed MG-63 tumor growth in the mice models without toxic and side effects.	[32, 33, 77]
Quercetin (Quer) complex with oxovanadyl (IV) [VO$(Quer)_2$EtOH]$_n$ (VOQuer)	*MC3T3E1* (normal osteoblast cell line), *UMR106* (osteosarcoma). The complexation of quercetin does not improve its potential anticarcinogenic properties. The complex was more cytotoxic toward normal osteoblasts. VOQuer interacts with two markers of osteoblastic differentiation; it stimulates type I collagen production and inhibits bovine ALP-specific activity; QuerVO stimulated the phosphorylation of ERKs in a dose-response manner, showing that the mitogenic effect of the complex in osteoblasts may involve the ERK pathways. VOQuer shows potential for promoting osteoblast differentiation.	[78]
cis-[Pt$(PPh_3)_2$(3-Hfl)]Cl **(1)** *cis*-[Pt$(PPh_3)_2$(etga)] **(2)** PPh = triphenylphosphine, 3-Hfl = 3-hydroxyflavone monoanion, etga = etilgalat dianion	*U87* (glioblastoma): IC_{50}(μM) values: 3-Hfl: 27.5 ± 2.3; **(1)**: 26.3 ± 2.1; etga: 97.7 ± 2.6; **(2)**: 123.7 ± 3.8; cisplatin: 1.76 ± 0.22; *MCF-7* (breast tumor): IC_{50}(μM) values: 3-Hfl: 108.1 ± 3.5; **(1)**: 55.5 ± 1.7; etga: > 200; **(2)**: >200; cisplatin: 14 ± 3.	[79]

Complex	Comments	Ref.
Ru(II) *cis*-dichlorobis(3-imino-2-methoxy-flavanone) **(1)** Ru(II) *cis*-dichlorobis(3-imino-2-ethoxy-flavanone) **(2)** Ru(II) *cis*-dichloro(3-nitrozoflavone)(3-hydroxyiminoflavanone)**(3)**	*A549*: IC_{50}(μM) values: cisplatin: 3.8 ± 0.8; **(1)**: ~100; **(2)**: 5.3 ± 0.4; **(3)**: 3.8 ± 0.3; *A2780* (ovarian cancer): IC_{50}(μM) values: cisplatin: 0.2 ± 0.1; **(1)**: 39.6 ± 3; **(2)**: 2.5 ± 0.2; **(3)**: 1.8 ± 0.1; *A2780cis* (cisplatin-resistant subline): IC_{50}(μM) values: cisplatin: 16.8 ± 1.5; (1): 62.5 ± 16; (2): 4.6 ± 0.2; (3): 1.5 ± 0.04; *Toledo* (diffuse large B-cell lymphoma): IC_{50}(μM) values: cisplatin: 0.5 ± 0.07; **(1)**: 13.9 ± 1.2; **(2)**: 0.5 ± 0.1; **(3)**: 0.6 ± 0.04; *Toledo-cis* (cisplatin-resistant subline): IC_{50}(μM) values: cisplatin: 8.3 ± 0.6; **(1)**: 56.6 ± 2.8; **(2)**: 2.9 ± 0.2; **(3)**: 2.8 ± 0.1. *Lymphocytes*: IC_{50} (μM) values: cisplatin: 0.2 ± 0.1; **(1)**: 19.4 ± 3; **(2)**: 3.4 ± 0.3; **(3)**: 1.6 ± 0.2. The complexes had minor effects on hemostasis or on the red blood cell lysis *in vitro*, at cytotoxic concentrations and are therefore unlikely to cause hematologic disorders *in vivo*.	[80]
Ru(II) complex with η^6-*p*-cymene and 3-hydroxyflavone derivatives	*CH1 (ovarian carcinoma), SW480 (colon carcinoma, A549 (non-small-cell lung carcinoma), 5637 (human urinary bladder), LCLC-103H (human large-cell lung), DAN-G (human pancreatic carcinoma cell lines).* The IC_{50} values were in the low micromolar range. The chemosensitive CH1 cell line was very sensitive to the complexes with IC_{50} values < 7.9 μM; for SW480, the IC_{50} values: 3.4–26 μM. The lowest cytotoxic potency was found for *A549* (IC_{50}: 8.6–51 μM). Some of the complexes have an influence on the cell cycle distribution; at concentrations around the IC_{50} values of the complexes, an increase in the cell fraction in G0/G1 phase was observed. Most of the complexes strongly inhibit CDK2, inhibit topoisomerase IIα to a greater extent than the corresponding free ligands (the activity on topo-IIα correlates with the cytotoxic effect of the complexes).	[81]
Quercetin complexes with Zn(II), Mn(II) $[Zn(que)_2(H_2O)_2]$ **(1)** $[Mn(que)_2(H_2O)_2]$ **(2)**	*HepG2*: IC_{50}(μM) values: $(que)_2$: 13.3 ± 1.0; **(1)**: 5.46 ± 0.36; **(2)**: 8.0 ± 0.3; *SMMC-7221* (hepatocarcinom): IC_{50}(μM) values: $(que)_2$: 13.3 ± 1.0; **(1)**: 7.66 ± 0.30; **(2)**: 8.0 ± 0.3; *A549*: IC_{50}(μM) values: $(que)_2$:13.3 ± 1.0; (**1**): 10.0 ± 0.45; **(2)**: 8.0 ± 0.3. The antitumor activity of **(2)** may be partially attributed to the interaction with the GC-rich DNA sequences and to DNA protein-binding interactions. These processes lead to downregulation of survivin gene expression, caspase activation, and induction of apoptosis. HepG2 cells had undergone morphological changes typical of apoptosis, characterized by nuclear shrinkage, chromatin condensation, and fragmentation subsequent to exposure to complex **(1)**. The cytotoxic effect is partially attributed to intercalation between DNA base pairs.	[82, 83]
Chrysin **(1)**, apigenin **(2)**, genistein **(3)** homoleptic Cu(II) Complexes **(4)–(6)**, respectively	*518A2* (melanoma): IC_{50}(μM) values: **(1)**: > 50; **(2)**: > 50; **(3)** > 50; **(4)**: 10.9 ± 1.6; **(5)**: 13.2 ± 1.1; **(6)**: 10.9 ± 1.4; *HCT-116* (colon carcinoma): IC_{50}(μM) values: **(1)**: > 50; **(2)**: > 50; **(3)** > 50; **(4)**: 14.8 ± 2.7; **(5)**: 15.8 ± 2.5; **(6)**: 10.4 ± 1.6; *KB-V1/Vbl* (cervix carcinoma): IC_{50}(μM) values: **(1)**: 12.5 ± 2.1; **(2)**: 20.6 ± 1.7; **(3)** 28.8 ± 3.0; **(4)**: 4.6 ± 0.5; **(5)**: 8.0 ± 1.2; **(6)**: 6.7 ± 0.5; *MCF-7/Topo* (breast carcinoma): IC_{50}(μM) values: **(1)**: 28.2 ± 6.1; **(2)**: 31.2 ± 0.9; **(3)** 37.0 ± 3.0; **(4)**: 7.8 ± 1.5; **(5)**: 11.8 ± 0.7; **(6)**: 8.5 ± 1.4; The cytotoxic activity of the complexes was correlated with an arrest of the cell cycle of *518A2* cells at the G2/M transition. The complexes gave better results than the free flavonoids in decreasing the migration propensity of *518A2* cells in wound-healing assays. The antimetastatic effects of complex **(6)** derive from the remodeling of the actin cytoskeleton and the increase in cadherin-catenin complex formation, factors that favor cell-cell adhesion. Complex (**6**) decreased the expression and secretion of the metastasis-related matrix metalloproteinases MMP-2 and MMP-9. Thus, the coordination of apigenin and genistein to Cu(II) enhances the antitumoral properties of the free flavonoids and expands their mechanistic range.	[84]

Complex	Comments	Ref.
Chiral L/D-valine (val) quercetin (Q) organotin(IV) complexes $[(CH_3)_2Sn(Q)(val)]$ $\mathbf{1}_{L/D}$ $[(C_6H_5)_2Sn(Q)(val)]$ $\mathbf{2}_{L/D}$	*HeLa*: IC_{50} (μg mL^{-1}) values: < 10; *MCF-7*: IC_{50} (μg mL^{-1}) values: < 10; *HepG2*: IC_{50} (μg mL^{-1}) values: $\mathbf{1}_L$: 34.6; $\mathbf{2}_L$: < 10; *MIA-Pa-Ca-2* (pancreas cancer): IC_{50} (μg mL^{-1}) values: < 10; The mechanistic activity of the complexes appears to involve interaction with topoisomerase I and DNA.	[85]

ALP: alkaline phosphatase; ERK: extracellular-regulated kinase; CDK2: cyclin A protein kinase.

Table 3. Metal complexes of flavonoids with antitumor activity.

It should be kept in mind that with the failure of ASA404/vadimezan (Antisoma/Novartis) in a phase III trial for advanced non-small-cell line cancer when given in combination with carboplatin and taxol [86], there are no more benzopyran-4-one derivatives strong candidates for anticancer drugs. The research regarding the antitumor properties of flavonoid metal complexes offers promising results and these should be further improved in order for the complexes to enter clinical trials.

5. Interactions of flavonoids metal complexes with proteins

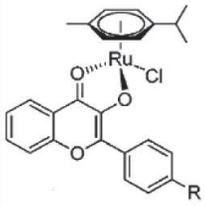
Protein binding can influence the blood levels and the pharmacokinetic behavior of a drug and possibly its pharmacologic and toxicologic profiles. Human serum albumin (HSA) is quantitatively ~55% of total serum proteins. Analyses of the crystal structure of the protein indicate that the main binding sites in HSA are located in the hydrophobic cavities of subdomains II and III of site A. These binding sites are known as Sudlow I and II, respectively. The remaining single tryptophan in HSA structure is located within the site's Sudlow I (Trp-214) [87]. Serum albumin (SA) is involved in blood transport for many compounds and metal ions. The interactions of a drug with SA play a major role in drug efficacy. Flavonoids and their metal complexes interact in the microenvironment surrounding the tryptophan residue of SA.

Transferrin (Tf) is a monomeric glycoprotein, containing two main metal ion binding sites: the N-terminal lobe and the C-terminal lobe, similar in structure, each binding one Fe(III) ion. It has been found that iron-binding sites in the serum Tf are only saturated to an extent of 39% of Fe(III), meaning that the free lobes can bind other metal ions [88]. Cancer cells, as active and rapidly proliferating cells, express high levels of transferrin receptors. Consequently, transferrin has been explored as a potential drug carrier for targeted delivery into tumor cells [89].

Moreover, human topoisomerase II-α (topo II-α) is currently a target for anticancer chemotherapy. Topo II-α is involved in DNA transcription, replication, and chromosome segregation. Although these biological functions are vital for insuring genomic integrity, the ability to inhibit topo II-α and generate enzyme-mediated DNA damage in cancer cells is an effective strategy in antitumor therapy [90]. Electrostatic forces, hydrogen bonds, and van der Waals interactions are involved in the interactions of flavonoid metal complexes and proteins [72].

Flavonoids and their metal complexes bind bovine serum albumin (BSA) or human (HSA), in vitro, with different affinities (**Table 4**).

Complex	Comments	Ref.
Diosmin-oxovanadyl (IV) complex $[VO(dios)(OH)_3]$ $Na_{5.}6H_2O$ (VOdios)	Diosmin and VOdios interactions with BSA follow a static mechanism, a ratio of 1: 1 compound: protein; the interaction is enabled via hydrogen bonds and van der Waals forces. At 298 K: $K_{b\ dios} = 1.84 \pm 0.32 \times 10^4\ M^{-1}$ $K_{b\ VOdios} = 55.3 \pm 0.07 \times 10^5\ M^{-1}$	[35]
Luteolin- oxovanadyl (IV) complex $[VO(lut)(H_2O)_2]$ $Na{\cdot}3H_2O$ (VOlut)	Luteolin interacts with the microenvironment around tryptophan in BSA, by electrostatic forces; the complex interacts with the protein through hydrogen bonds and van der Waals forces. The interaction takes place in a ratio of 1: 1 compound: protein through a static mechanism. At 298 K: $K_{b\ lut} = 65.10 \pm 0.90 \times 10^6\ M^{-1}$ $K_{b\ VOdios} = 79.43 \pm 0.56 \times 10^6\ M^{-1}$	[75]
Naringenin-oxovanadyl (IV) complex $[VO(nar)_2]{\cdot}2H_2O$ (VOnar)	The interaction takes place in a ratio of 1:1 compound:protein through a static mechanism. Complexation lowered the binding affinity to BSA of naringenin, probably due to steric hindrance. At 298 K: $K_{b\ nar} = 10.20 \pm 0.30 \times 10^4\ M^{-1}$ $K_{b\ VOnar} = 0.31 \pm 0.01 \times 10^4\ M^{-1}$	[76]
Quercetin and morin and their sulfonic derivatives-oxovanadyl (IV) complexes $VO(que)_2$ $VO(mor)_2$ $VO(que^S)_2$ $VO(mor^S)_2$	In the systems with apo-human transferrin (apo-HTF) and albumin (HSA), $VO(que)_2$ and $VO(Que^S)_2$ are stable, while VO $(mor)_2$ and $VO(mor^S)_2$ undergo displacement reactions, when the species $(VO)_x$(HSA) and (VO)(apo-HTF)/ $(VO)_2$(apo-HTF) and VO-apo-HTF-mor^S and mor^S-VO-HAS are formed. The complexes interact strongly with the proteins by the formation of hydrogen bonds with polar groups on the protein surface. $VO(que)_2$/$VO(Que^S)_2$ does not interact with hemoglobin, while $VO(mor)_2$/$VO(mor^S)$ forms adducts with hemoglobin (Hb).	[91]
Baicalein-Al(III) complex (ALBC)	The results of the competitive binding and molecular-docking studies indicate that BC binds to HSA at site I (subdomain IIA), while ALBC binds mainly at site II (subdomain IIIA). BC binding had a greater influence than ALBC on the secondary structure of the protein. At 297 K: $K_{b\ BC} = 1.73 \times 10^5\ M^{-1}$ $K_{b\ ALBC} = 1.67 \times 10^5\ M^{-1}$	[92]
Dihydromyricetin Mn(II), Cu(II) and Zn(II) complexes MnDMY CuDMY ZnDMY	DMY-BSA interaction is achieved by van der Waals forces and hydrogen bonds, while complexes bind through hydrophobic and hydrogen-bonding forces (conclusions based on thermodynamic values for parameters). At 300 K: $K_{b\ DMY} = 1.30 \times 10^5\ M^{-1}$ $K_{b\ MnDMY} = 2.13 \times 10^5\ M^{-1}$ $K_{b\ CuDMY} = 2.95 \times 10^5\ M^{-1}$ $K_{b\ ZnDMY} = 7.76 \times 10^4\ M^{-1}$	[93]
Morin-La(III) complex (La-Mo)	La-mo-HSA interaction was studied by means of spectrofluorometry and circular dichroism. It has been found that La-mo is an efficient interaction with HSA hydrogen bonding and van der Waals forces. The thermodynamic parameters (ΔG, ΔH, ΔS) that characterize the interaction had negative values, implying that the binding is thermodynamically favorable and the degree of reversibility is modest. Circular dichroism spectra show a reduction in the α-helix-type structures from 60.0 to 56.9% and an increase in the β-chain-type structures from 6.0 to 7.1% in HSA. Molecular-docking studies show that La-mo competes with warfarin site Sudlow I of subdomain II in HSA structure. At 299 K: $K_{b\ La\text{-}Mo} = 1.5752 \pm 0.007 \times 10^5\ M^{-1}$	[94]

Complex	Comments	Ref.
Ru(II)-η^6-*p*-cymene complex  R=CH_3, F or Cl	The complex interacts with topoisomerase II-α and the interaction depends on the substituent located at the *para*-position of the phenyl ring. The complex where R=Cl is the most potent topoisomerase inhibitor. The complexes showed better activity than the ligands.	[95]
Quercetin-Cu^{II}-Sn_2^{IV} heterobimetallic complex	The complex is a potent inhibitor of topoisomerase I at 30 μM.	[96]

K_b: binding constant; K_i: inhibition constant.

Table 4. Selection of flavonoid metal complexes-protein interactions studies.

6. Interactions of flavonoids metal complexes with nucleic acids

The ability of small molecules to interact with DNA ranks among the most important mechanisms of action enabling antitumor activity, since intercalation between adjacent base pairs inhibits DNA replication. Most of the flavonoids and their metal complexes show affinity toward nucleic acids. Flavonoids bind DNA as a result of electrostatic interactions, as is the case of quercetin [97] and morin [98 and references therein]. Their complexes, on the other hand, are bulkier, and display more diversified mechanisms of interaction with DNA, including "major" or "minor groove" binding and/or intercalation. Due to their structural planarity, flavonoid complexes are prone to act as intercalators [99]. Moreover, the emergence of electrostatic interactions between the metal cation and anionic phosphate groups of DNA structure stabilizes the adducts formed between the complexes and DNA. It is considered that the DNA base pairs remove the flavonoid molecules in the metal complex, since the binding affinity between the negatively charged phosphate groups and the positively charged metal ions is stronger than that between the flavonoid molecule and the metal center [100, 101]. In most cases, active compounds possess quasi-planar structures, with a medium-sized planar area and hydrophobic character [82]. A selection of the metal complexes of flavonoids that interact with DNA is presented in **Table 5**.

Another aspect regarding DNA interaction refers to the complexes' cleavage activity. This property can benefit their antitumor activity, but can also cause oxidative DNA damage (and consequently cell death) in normal cells [22]. Therefore, efforts toward increasing the complexes' selectivity against cancer cells are of prior importance.

The development of electrochemical DNA biosensors has been of high interest in this field, since metal flavonoid complexes show promising results in DNA recognition. Flavonoid complex-based biosensors can be useful in several domains, such as transducing DNA hybridization, drug design, and diagnosis [102, 103, 105].

Complex	Comments	Ref.
Fe(II)-quercetin complex $Fe(quer)_2$	The interaction of the complex with DNA occurs in a moderate intercalative manner. $Fe(quer)_2$ shows cleavage activity on plasmid DNA (pBR322) under physiological conditions, via oxidative pathway.	[40]
Ni(II)-rutin (R) complex metal:ligand molar ratio 1:2 (NiR)	The interaction of NiR with DNA was studied using fluorescence spectra and agarose gel electrophoresis. The complex can intercalate moderately between DNA base pairs and shows significant, dose-dependent cleavage activity on pBR322 plasmid DNA from the SC form to the NC form.	[52]
Fe(III) chlorobis(flavonolato) (methanol) complex metal:ligand molar ratio 1:2 Fe(III)-(3hf)	The complex shows cleavage activity toward CT-DNA via an oxidative mechanism with higher efficacy in the presence of reducing agents (ascorbate/hydrogen peroxide).	[101]
Cd(II)-morin complex $Cd(mor)_2$	The interaction with salmon sperm dsDNA was studied by means of electrochemical methods. $Cd(mor)_2$ can intercalate into the double-helix DNA; according to the Hill model for cooperative binding, the equilibrium dissociation constant and the binding stoichiometry were calculated to be $K = 2.5 \times 10^{-5}$ M and $m = 1.761$, respectively.	[102]
Co(II)-morin complex $Co(mor)_2$	Competitive experiments, viscosity, and electrochemical studies indicate that the complex binds to DNA via a weak partial intercalation. $K_b = 2 \times 10^3$ M^{-1} at 20°C.	[103]
Morin **(1)** Cu(II)-morin complex **(2)** Morin-β-CD **(3)**	Intercalation was proposed as the mode of binding of the ligand, the complex with salmon sperm dsDNA via cyclic and square wave voltammetry, UV-vis spectroscopy techniques. K_b values: **(1)**: 1.58, **(2)**: 2.29, **(3)**: 3.20×10^5 M^{-1} at 298 K. Other studies indicate that morin interacts with DNA in a non-intercalative manner [98].	[104]
Cu(II)-rutin (R) complex Cu_2R_3	The interaction of Cu_2R_3 with salmon sperm dsDNA was studied by means of cyclic voltammetry and fluorescence spectroscopy. The complex interacts with DNA via intercalation and nonspecific electrostatic interaction. Cu_2R_3 was used for the construction of an electrochemical DNA biosensor for DNA hybridization detection, showing relatively good sensitivity and selectivity.	[105]
Cu(II)-hesperetin complex	$K_b = 1.5 \times 10^6$ M^{-1} The UV-vis, fluorescence and CD spectral measurements revealed that both the complex and the ligand interact with CT-DNA via intercalation. The binding affinity of the complex is stronger than that of free ligand.	[59, 70]
Cu(II)-quercetin complex metal:ligand molar ratio 1:2	By means of UV-vis spectrophotometry, cyclic voltammetry, and synchronous fluorescence spectroscopy, an intercalative binding mode was proposed. $K_b = 1.82 \pm 0.2 \times 10^5$ M^{-1} The equilibrium constant of the exchange process in the intercalation reaction was found to be approximately 5×10^{-1}; 35% of the bound complex was not involved in intercalation.	[106]
Tb(III)/Eu(III)-quercetin system	A sensitive method for the determination of CT-DNA is proposed based on the quenching effect of DNA on the RLS intensity of Tb(III)/Eu(III)-quercetin system.	[100]

Complex	Comments	Ref.
Chiral L/D-valine (val) quercetin (Q) diorganotin(IV) complexes $[(CH_3)_2Sn(Q)(val)]$ $\mathbf{1}_{L/D}$ $[(C_6H_5)_2Sn(Q)(val)]$ $\mathbf{2}_{L/D}$	UV-vis, fluorescence titrations, thermal denaturation, and circular dichroism studies revealed the electrostatic mode of DNA binding of the complexes, although partial intercalation into the DNA helix and hydrophobic interactions cannot be excluded. K_b values (: $\mathbf{1}_L$: 2.17×10^5 M^{-1}; $\mathbf{1}_D$: 1.00×10^4 M^{-1}; $\mathbf{2}_L$: 4.74×10^5 M^{-1}; $\mathbf{2}_D$: 1.40×10^4 M^{-1}) revealed that the L-enantiomers of exhibited exceptionally high-binding propensity as compared to their D-enantiomers. $\mathbf{1}_L$ and $\mathbf{2}_L$ exhibit supercoiled DNA cleavage ability mediated by single strand breaks.	[85]
La(III)-chrysin complex	$K_{b\ chrysin} = 1.29 \times 10^6$ M^{-1}; $K_{b\ complex} = 5.44 \times 10^5$ M^{-1} Spectrophotometric methods and viscosity measurements indicated that La(III) complex and chrysin can both bind to DNA by intercalation modes.	[107]
Eu(III)-quercetin complex $Eu(quer)_3$	The CT-DNA interactions were studied using cyclic voltammetry and double potential step chronocoulometry at glass carbon electrode for the surface method. Quercetin binds to DNA mainly by electrostatic interaction and the complex binds to DNA by means of intercalation and electrostatic forces. For the dsDNA-modified GCE systems, the following parameters were obtained: $\Gamma_{s\ quercetin} = 2.28 \pm 0.2 \times 10^{-10}$ mol/cm^3 $n_{quercetin} = 1.2$ $\Gamma_{s\ Eu(quer)3} = 1.65 \pm 0.2 \times 10^{-10}$ mol/cm^3 $n_{Eu(quer)3} = 1.8$	[97]
Mn(II)-quercetin complex metal:ligand molar ratio 1:2	UV/VIS, fluorescence spectroscopy, and viscosity measurements were carried out. The results indicate that the complex binds preferentially in the GC-rich regions via an intercalative mode.	[83]
Zn(II)-quercetin complex metal:ligand molar ratio 1:2	The complex promotes plasmid DNA cleavage, producing single- and double-DNA strand breaks. The amount of conversion of the SC form to the NC form depends on the concentration of the complex and the duration of incubation with DNA. The rate of conversion of SC to NC is 1.68×10^{-4} s^{-1} at pH 7.2 (100 μM complex).	[108]
Cu^{II}-$\mathbf{Sn}^{IV}_2$-quercetin Zn^{II}-$\mathbf{Sn}^{IV}_2$-quercetin	The heterobimetallic-type complexes form electrostatic interactions with DNA (between Sn^{IV} and the phosphate groups) and covalent bond between the metal center and nitrogenous bases. The complex Cu^{II}-$\mathbf{Sn}^{IV}_2$-quercetin exhibits nuclease and SOD-mimetic activity.	[96]

ds: double-stranded; CT-DNA: calf thymus DNA; RLS: resonance light scattering; Γ_s: saturation coverage value; GC: guanine-cytosine; SC: supercoiled; NC: nicked circular form.

Table 5. Selection of flavonoid metal complexes-DNA interaction studies.

Regarding the interaction of the complexes with RNA, a few studies have been cited in the literature. La(III)-quercetin complex enhances binding to plant viral satellite dsRNA [109]. Both quercetin and the complex interact with dsDNA, dsRNA, and ssRNA. The affinities of La(III)-quercetin for dsDNA and dsRNA were significantly higher compared to the free ligand, revealing significant impact of La(III) in binding to polynucleotides, most likely due to the electrostatic interactions between La(III) and the phosphate groups surrounding binding sites. Similar results were observed for interactions of the La(III)-quercetin complex with ssRNA [110].

Undisputedly, there is a consistent amount of experimental evidence regarding the interaction of flavonoids and their metal complexes with nucleic acids. However, some details with respect to the binding sites in the DNA structure need further investigations. There appears that the complexes possess higher affinity toward GC-rich sequences in DNA [111], but this assumption needs to be backed up by more data.

7. Perspectives in the formulation of flavonoids metal complexes

In order to enhance the water solubility and to control the release of flavonoids metal complexes, many efforts have been focused on the preparation of cyclodextrin complexes, or of novel micro- and nano-carriers, such as liposomes and organic compounds-inorganic particles hybrid materials (HMs). In the following subchapter, the most important systems developed for the inclusion of flavonoids metal complexes with antioxidant or antitumor activity will be reviewed, as well as the systems that include flavonoids with antitumor activity based on the complexation process between flavonoid and metal ions.

7.1. Liposomal systems

Flavonoids' ability to penetrate into the hydrophobic regions of lipid bilayers in biological membranes is a key factor to prevent peroxidation of unsaturated double bonds. In this regard, the lipophilicity of flavonoids is essential for an adequate penetration. According to Tweedy's chelation theory, the polarity of the metal ion is reduced, as a consequence of chelation, mainly because of the partial sharing of its positive charge with the ligand's donor groups and possible electron delocalization over the entire ring. Consequently, the lipophilic character of the chelates increases, favoring their permeation through the lipid layers of biological membranes [112]. For two complexes of quercetin and taxifolin with Fe(II), it was assumed that the oxygen charges are generally decreases, while the main negative charge is localized on the iron atom. Thus, after chelating the metal ion, the polarity of flavonoid molecules generally decreased, while the iron atom becomes the most polar and hence hydrophilic part of the molecule. Overall, the lipophilicity of the complexes is considerably larger than that of the corresponding free flavonoids [113, 114].

On the other side, the hydrophobicity of flavonoids chelates dramatically reduces the water solubility, which restricts their medical applications. Integration of these complexes into liposomes may increase their bioavailability and improve the therapeutic effect.

The interaction study of quercetin-iron complexes with dimyristoylphosphatidylcholine (DMPC) or palmitoyl-oleoyl phosphatidylethanolamine (POPE) multilamellar liposomes revealed that, during preparation, quercetin should be added first to the suspension of liposomes [115]. It was presumed that quercetin can increase the permeability of lipid bilayers to iron cations, showing ionophore activity toward iron cations.

7.2. Cyclodextrins

The inclusion into cyclodextrins is a convenient alternative to solve the problems related to the low solubility of hydrophobic drugs, such as flavonoid complexes. Inclusion of Cu(II) and

Cr(III) complexes of flavonoids morin, quercetin, and 6-hydroxyflavone into β-cyclodextrin led to an enhancement of aqueous solubility [116]. The anticancer activity of metal-flavonoid complexes was evaluated in terms of dsDNA binding in the environment of beta-cyclodextrin, and it was revealed that DNA could bind Cu-flavonoid-βCD through intercalation and Cr-flavonoid-βCD via an electrostatic-binding mode.

7.3. Organic/inorganic hybrid nanosystems

Based on the property of flavonoids to reduce metal ions such as Ag(I) and Au(III), some hybrid systems of ***flavone/metal nanoparticles*** have been developed. It was suggested that flavanones can be adsorbed on the surface of metallic nanoparticles through the interaction of the metals with the carbonyl groups or π electrons in the flavonoid structures [117].

The effect of 3-hydroxyflavone (3-HF) in a silver nanoparticles (SNPs) complex on the cell viability and on the cell morphology of L929 mouse fibroblast cells was studied *in vitro*. The contribution of the carrier protein BSA to 3-HF properties has also been investigated. Determination of the cell viability using MTT assay revealed that 3-HF in BSA/SNPs systems presented no cytotoxic effect in L929 mouse fibroblast cells at any of the tested concentrations [118].

In order to enhance the interaction efficacy with biomacromolecules and therefore increase its therapeutic potential, morin was conjugated with citrate-coated Au nanoparticles (M-C-AuNPs). Interactions of M-C-AuNPs and C-AuNPs with BSA were studied in order to compare the efficiency of M-C-AuNPs and C-AuNPs in biological systems. It was found that the binding affinity toward BSA of M-C-AuNPs is significantly higher than that of C-AuNPs', indicating that M-C-AuNPs might show better BSA interaction efficiency, better biocompatibility, and chemical stability than C-AuNPs [119].

Taking into account the potential biomedical applications, for example, targeted drug delivery, several flavonoids with antioxidant and antitumor activities have been conjugated with ***magnetic nanoparticles***, mainly Fe_3O_4. Flavonoid molecules can bind to Fe_3O_4 via the hydroxyl substituents in their deprotonated form. Most of the biomedical applications of magnetic nanoparticles require surface modification for drug loading or anchoring linkers in support of sustained drug release. Surface functionalization with PEG (polyethylene glycol), PVP (polyvinylpyrrolidone), PVA (polyvinyl acetate), peptides, carbohydrates, proteins, and so on facilitates the drug loading and controlled release, and also controls the stability of the system [120].

Quercetin-conjugated superparamagnetic Fe_3O_4 nanoparticles were investigated for the *in vitro* cytotoxic activity on breast cancer cell lines. The MTT assay revealed that the dextran-coated Fe_3O_4 nanoparticles did not exhibit notable toxicity against MCF7 cells, whereas the cytotoxicity of quercetin-conjugated Fe_3O_4 nanoparticles increased significantly in comparison with the free quercetin [120]. The results sustain that the quercetin-conjugated Fe_3O_4 nanoparticles are promising anticancer agents for targeted drug delivery.

A drug delivery methodology was proposed to study a new quercetin release system in the form of magnetite-quercetin-copolymer (MQC), as perspective of targeting specific organs within the body. The quercetin-magnetite nanoparticles (Fe_3O_4) system was incorporated into a triblock copolymer of ethylene oxide and oxyphenylethylene, as a model of drug carrier system for anticancer agents [121].

Furthermore, quercetin loading on ***mesoporous carriers*** was performed in order to enable the sustained delivery of the bioactive compound. Mesoporous nanosized silicas are widely used as carriers for drug delivery. However, the appropriate chemical surface modification of the mesoporous matrix is essential, taking into account that the silanol groups of the silica surface do not possess sufficient selectivity to adsorb drug molecules with different functionalities [122]. Quercetin was loaded on the pure silica and Zn-modified mesoporous MCM-41 and SBA-16 supports, and the formation of complexes between quercetin and pure siliceous or Zn-modified MCM-41 and SBA-16 mesoporous silica was determined. Quercetin has a higher binding affinity for the Zn^{2+} cation than to the silanol groups. Therefore, the release of quercetin is easier from the silicate samples containing only superficial silanol groups than from the Zn-modified samples. The obtained mesoporous delivery systems with Zn-quercetin complex showed promising results for further use in dermal formulations [123].

Natural zeolite of the clinoptilolite type (CT, particle size of up to 200 μm) and its modified forms with different concentrations (0.06–5%) of the pharmaceutically active compounds quercetin and quercetin dihydrate (QD) have been investigated for their anticancer activity. Carcinoma cell lines Jurkat, CEM, HeLa, MCF7, A549, and MDA were treated with various amounts of natural clinoptilolite and their modified forms CTQ and CTQD. Incorporation of the flavonoids quercetin and quercetin dihydrate with antiproliferative activity had no synergic effect on the zeolite cytotoxicity, but the protective effect of cancer cells. The tumor cell lines studied after the application of modified zeolite CTQ or CTQD had lower antiproliferative activity in comparison with the natural zeolite of the clinoptilolite-type CT. The modified zeolite CTQD had greater antiproliferative effects than modified zeolite CTQ [124].

8. Conclusions and future perspectives

There is an impressive number of studies with reference to the antitumor activity of flavonoids. However, even though the metal complexation of flavonoids generally results in enhanced antitumor activity, the number of studies regarding flavonoid metal complexes is much smaller. Moreover, none of the flavonoid metal complexes that have shown great antitumor activity has been included in clinical trials so far. This may happen due to the challenges implied by the study of the multiple possible mechanisms induced by the presence of the metal ion. Stability of the complexes in physiological context may also raise some important issues. Therefore, further studies are required to understand their mechanisms of action and their biotransformation in the human body.

Author details

Valentina Uivarosi* and Alexandra-Cristina Munteanu

*Address all correspondence to: valentina_uivarosi@yahoo.com

Department of General and Inorganic Chemistry, Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

References

[1] Kumar P, Kumar S, Tripathi MK, Mehta N, Ranjan R, Bhat ZF, Sing PK. Flavonoids in the development of functional meat products: A review. Veterinary World. 2013;**6**:573-578. DOI: 10.5455/vetworld.2013.573-578

[2] Symonowicz M, Kolanek M. Flavonoids and their properties to form chelate complexes. Biotechnology and Food Sciences. 2012;**76**:35-41.

[3] Tapas AR, Sakarkar DM, Kakde RB. Flavonoids as nutraceuticals: A review. Tropical Journal of Pharmaceutical Research. 2008;**7**:1089-1099. DOI: 10.4314/tjpr.v7i3.14693

[4] Beecher GR. Overview of dietary flavonoids: nomenclature, occurrence and intake. Journal of Nutrition. 2003;**133**:3248S–3254S.

[5] Leonarduzzi G, Testa G, Sottero B, Gamba P, Poli G. Design and development of nanovehicle-based delivery systems for preventive or therapeutic supplementation with flavonoids. Current Medicinal Chemistry. 2010;**17**:74-95. DOI: 10.2174/092986710789957760

[6] Laguerre M, Lecomte J, Villeneuve P. Evaluation of the ability of antioxidants to counteract lipid oxidation: Existing methods, new trends and challenges. Progress in Lipid Research. 2007;**46**:244-282. DOI:10.1016/j.plipres.2007.05.002

[7] Leopoldini M, Russo N, Toscano M. The molecular basis of working mechanism of natural polyphenolic antioxidants. Food Chemistry. 2011;**125**:288-306. DOI: 10.1016/j.foodchem.2010.08.012

[8] Cornard JP, Merlin JC. Comparison of the chelating power of hydroxyflavones. Journal of Molecular Structure 2003, **651**-**653**:381-387. DOI: 10.1016/S0022-2860(02)00655-5

[9] Block G. The data support a role for antioxidants in reducing cancer risk. Nutrition Reviews. 1992;**50**:207-213. DOI: 10.1111/j.1753-4887.1992.tb01329.x

[10] Elangovan V, Sekar N, Govindasamy S. Chemoprotective potential of dietary bioflavonoids against 20-methylcholanthrene-induced tumorigenesis. Cancer Letters. 1994;**87**:107-113. DOI: 10.1016/0304-3835(94)90416-2

[11] Le Marchand L. Cancer preventive effects of flavonoids—a review. Biomedicine and Pharmacotherapy. 2002;**56**:296-301. DOI: 10.1016/S0753-3322(02)00186-5

[12] Selway JW. Antiviral activity of flavones and flavans. Progress in Clinical and Biological Research. 1986;**213**:521-536.

[13] Middleton E Jr. Effect of plant flavonoids on immune and inflammatory cell function. Advances in Experimental Medicine and Biology. 1998;**439**:175-182.

[14] Gomes A, Fernandes E, Lima JL, Mira L, Corvo ML. Molecular mechanisms of anti-inflammatory activity mediated by flavonoids. Current Medicinal Chemistry. 2008;**15**:1586-1605. DOI: **10**.2174/092986708784911579

[15] Gabor M. Anti-inflammatory and anti-allergic properties of flavonoids. Progress in Clinical and Biological Research. 1986;**213**:471-480.

[16] Facino RM, Carini M, Aldini G, Berti F, Rossoni G, Bombardelli E, Morazzoni P. Diet enriched with procyanidins enhances antioxidant activity and reduces myocardial post-ischemic damage in rats. Life Sciences. 1999;**64**:943-949. DOI: 10.1016/S0024-3205(98)00605-5

[17] Herteg MG., Feskens EJM, Hollmen PCH, Katan MB, Kromhout D. Dietary flavonoids and risk of coronary heart disease. Lancet.1993;**342**:1007-1011

[18] Hodgson JM. Tea flavonoids and cardiovascular disease. Asia Pacific Journal of Clinical Nutrition. 2008;**17**:288-290

[19] Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: An overview. The Scientific World Journal. 2013;Article ID 162750:16 pages. DOI: 10.1155/2013/162750

[20] Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: A review of probable mechanisms of action and potential applications. American Journal of Clinical Nutrition. 2001;**74**:418-25.

[21] Heim KE, Tagliaferro AR, Bobilya DJ. Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. Journal of Nutritional Biochemistry. 2002;**13**:572-84.

[22] Samsonowicz M, Regulska E. Spectroscopic study of molecular structure, antioxidant activity and biological effects of metal hydroxyflavonol complexes. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2017;**173**:757-771. DOI: 10.1016/j.saa.2016.10.031

[23] Galati G, O'Brien PJ. Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. Free Radical Biology & Medicine. 2004;**37**:287-303. DOI: 10.1016/j.freeradbiomed.2004.04.034

[24] Procházková D, Boušová I, Wilhelmová N. Antioxidant and prooxidant properties of flavonoids. Fitoterapia. 2011;**82**:513-523. DOI:10.1016/j.fitote.2011.01.018

[25] Cao G, Sofic E, Prior RL. Antioxidant and prooxidant behavior of flavonoids: Structure-activity relationships. Free Radical Biology & Medicine. 1997;**22**:749-760. DOI: 10.1016/S0891-5849(96)00351-6

[26] Hanasaki Y, Ogawa S, Fukui S. The correlation between active oxygens scavenging and antioxidative effects of flavonoids. Free Radical Biology & Medicine. 1994;**16**:845-850. DOI: 10.1016/0891-5849(94)90202-X

[27] Cherrak SA, Mokhtari-Soulimane N, Berroukeche F, Bensenane B, Cherbonnel A, Merzouk H, Elhabiri M. *In vitro* antioxidant *versus* metal ion chelating properties of flavonoids: A structure-activity investigation. PLoS One. 2016;**11**:e0165575 DOI: 10.1371/journal.pone.0165575

[28] Nakagawa HK, Hasumi JT, Nagai K, Wachi M. Generation of hydroxide peroxide primarily contributes to the induction of Fe(II)-dependent apoptosis in Jurkat cells by (−)-epigallocatechin-3-gallate. Carcinogenesis. 2004;**25**:1567-1574. DOI: 10.1093/carcin/bgh168

[29] Lotito SB, Frei B. Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon. Free Radical Biology & Medicine. 2006;**41**:1727-1746. DOI: 10.1016/j.freeradbiomed.2006.04.033

[30] Roy S, Mallick S, Chakraborty T, Ghosh N, Singh AK, Manna S, Majumdar S. Synthesis, characterisation and antioxidant activity of luteolin–vanadium(II) complex. Food Chemistry. 2015;**173**:1172-1178. DOI: 10.1016/j.foodchem.2014.10.141

[31] Jiang J, Yao S, Cai H-H, Yang P-H, Cai J. Synthesis and synergetic effects of chrysin–organogermanium (IV) complex as potential anti-oxidant. Bioorganic & Medicinal Chemistry Letters. 2013;**23**:5727-5732. DOI: 10.1016/j.bmcl.2013.07.073

[32] Naso, L, Ferrer EG, Leyama L, Rojo T, Etcheverry SB, Williams P. Role of oxidative stress in the antitumoral action of a new vanadyl(IV) complex with the flavonoid chrysin in two osteoblast cell lines: relationship with the radical scavenger activity. Journal of Biological Inorganic Chemistry. 2010;**15**:889-902. DOI 10.1007/s00775-010-0652-z

[33] León IE J. Cadavid-Vargas F, Tiscornia I, Porro V, Castelli S, Katkar P, Desideri A, Bollati-Fogolin M, Etcheverry SB. Oxidovanadium(IV) complexes with chrysin and silibinin: Anticancer activity and mechanisms of action in a human colon adenocarcinoma model. Journal of Biological Inorganic Chemistry. 2015;**20**:1175-1191. DOI: 10.1007/s00775-015-1298-7

[34] Jabbari M, Gharib F. Solvent dependence on antioxidant activity of some water-insoluble flavonoids and their cerium(IV) complexes. Journal of Molecular Liquids. 2012;**168**:36-41. DOI:10.1016/j.molliq.2012.02.001

[35] Naso L, Martínez VR, Lezama L, Salado C, Valcarcel M, Ferrer EG, Williams PA. Antioxidant, anticancer activities and mechanistic studies of the flavone glycoside diosmin and its oxidovanadium(IV) complex. Interactions with bovine serum albumin. Bioorganic & Medicinal Chemistry. 2016;**24**:4108-4119. DOI: 10.1016/j.bmc.2016.06.053

[36] Ghosh N, Chakraborty T, Mallick S, Mana S, Singha D, Ghosh B, Roy S. Synthesis, characterization and study of antioxidant activity of quercetin–magnesium complex. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2015;**151**:807-813. DOI: 10.1016/j.saa.2015.07.050

[37] Dias K, Nikolaou S, De Giovani WF. The in vitro antioxidant properties of the Al-quercetin/βCD and Al-catechin/βCD inclusion compounds, rationalized in terms of their electrochemical behaviour. Medicinal Chemistry Research. 2012;**21**:2920-2925. DOI: 10.1007/s00044-011-9812-0

[38] Li S-P, Xie W-L, Cai H-H, Cai J-Y, Yang P-H. Hydroxyl radical scavenging mechanism of human erythrocytes by quercetin–germanium (IV) complex. European Journal of Pharmaceutical Sciences. 2012;**47**:28-34. DOI: 10.1016/j.ejps.2012.04.019

[39] Dehghan G, Khoshkam Z. Tin(II)–quercetin complex: Synthesis, spectral characterisation and antioxidant activity. Food Chemistry. 2012;**131**:422-426. DOI:10.1016/j.foodchem.2011.08.074

[40] Raza A, Xu X, Xia L, Xia C, Tang J, Ouyang Z. Quercetin-iron complex: Synthesis, characterization, antioxidant, DNA binding, DNA cleavage, and antibacterial activity studies. Journal of Fluorescence. 2016;**26:**2023-2031. DOI: 10.1007/s10895-016-1896-y

[41] Bukhari SB, Memon S, Tahir MM, Bhanger MI. Synthesis, characterization and investigation of antioxidant activity of cobalt–quercetin complex. Journal of Molecular Structure. 2008;**892**:39-46. DOI:10.1016/j.molstruc.2008.04.050

[42] Pękal A, Biesaga M, Pyrzynska K. Interaction of quercetin with copper ions: Complexation, oxidation and reactivity towards radicals. Biometals. 2011;**24**:41-49. DOI: 10.1007/s10534-010-9372-7

[43] Bukhari SB, Memon S, Mahroof-Tahir M, Bhanger MI. Synthesis, characterization and antioxidant activity copper–quercetin complex. Spectrochimica Acta Part A. 2009;**71**:1901-1906. DOI :10.1016/j.saa.2008.07.030

[44] Ravichandran R, Rajendran M, Devapiriam D. Antioxidant study of quercetin and their metal complex and determination of stability constant by spectrophotometry method. Food Chemistry. 2014;**146**:472-478. DOI: 10.1016/j.foodchem.2013.09.080

[45] Zhou J, Wang L, Wang J, Tang N. Antioxidative and anti-tumour activities of solid quercetin metal(II) complexes. Transition Metal Chemistry. 2001;**26**:57-63. DOI: 10.1023/A:1007152927167

[46] de Souza RFV, De Giovani WF. Antioxidant properties of complexes of flavonoids with metal ions. Redox Report. 2004;**9**:97-104. DOI: 10.1179/135100004225003897

[47] Zhou J, Wang L, Wang J, Tang N. Synthesis, characterization, antioxidative and antitumor activities of solid quercetin rare earth(III) complexes. Journal of Inorganic Biochemistry. 2001;**83**:41-48. DOI: 10.1016/S0162-0134(00)00128-8

[48] Naso LG, Lezama L, Rojo T, Etcheverry SB, Valcarcel M, Roura M, Salado C, Ferrer EG, Williams PA. Biological evaluation of morin and its new oxovanadium(IV) complex as antioxidant and specific anti-cancer agents. Chemico-Biological Interactions. 2013;**206**:289-301. DOI: 10.1016/j.cbi.2013.10.006

[49] Panhwar QK, Memon S. Synthesis of Cr(III)-morin complex: Characterization and antioxidant study. The Scientific World Journal. 2014; Article ID 845208, 8 pages. DOI: 10.1155/2014/845208

[50] Panhwar QK, Memon S, Bhanger MI. Synthesis, characterization, spectroscopic and antioxidation studies of Cu(II)–morin complex. Journal of Molecular Structure. 2010;**967**:47-53. DOI: 10.1016/j.molstruc.2009.12.037

[51] Roy S, Majumdar S, Singh AK, Ghosh B, Ghosh N, MannaS, Chakraborty T, Mallik S. Synthesis, characterization, antioxidant status, and toxicity study of vanadium–rutin complex in balb/c mice. Biological Trace Element Research. 2015;**166**:183-200. DOI: 10.1007/s12011-015-0270-2

[52] Raza A, Bano S, Xu X, Zhang RX, Khalid H, Iqbal FM, Xia C, Tang J, Ouyang Z. Rutin–nickel complex: Synthesis, characterization, antioxidant, DNA binding, and DNA cleavage activities. Biological Trace Element Research. DOI: 10.1007/s12011-016-0909-7

[53] Afanas'ev IB, Ostrachovich EA, Korkina LG. Effect of rutin and its copper complex on superoxide formation and lipid peroxidation in rat liver microsomes. FEBS Letters. 1998;**425**:256-258. DOI: 10.1016/S0014-5793(98)00244-0

[54] Ikeda NE, Novak EM, Maria DA, Velosa AS, Pereira RM. Synthesis, characterization and biological evaluation of Rutin–zinc(II) flavonoid-metal complex. Chemico-Biological Interactions. 2015;**239**:184-191. DOI: 10.1016/j.cbi.2015.06.011

[55] Zhai G, Qu W, Yan Z, Zhu W, Duan Y, Wang J. Synthesis, spectral and antioxidant properties of tin(II)-rutin complex. Chemistry of Natural Compounds. 2014;**50**:624-628. DOI: 10.1007/s10600-014-1039-0

[56] Panhwar QK, Memon S. Synthesis, characterization and antioxidant study of Tin(II)–rutin complex: Exploration of tin packaging hazards. Inorganica Chimica Acta. 2013;**407**:252-260. DOI: 10.1016/j.ica.2013.08.001

[57] Panhwar QK, Memon S. Synthesis, characterization, and antioxidant study of Cr(III)–rutin complex. Chemical Papers. 2014;**68**:614-623. DOI: 10.2478/s11696-013-0494-6

[58] Qi Y, Jiang M, Cui Y-L, Zhao L, Liu S. Novel reduction of Cr(VI) from wastewater using a naturally derived microcapsule loaded with rutin–Cr(III) complex. Journal of Hazardous Materials. 2015;**285**:336-345. DOI: 10.1016/j.jhazmat.2014.12.008

[59] Tamayo LV, Gouvea LR, Sousa AC, Albuquerque RM, Teixeira SF, de Azevedo RA, Louro SRW, Ferreira AK, Beraldo H. Copper(II) complexes with naringenin and hesperetin: cytotoxic activity against A 549 human lung adenocarcinoma cells and investigation on the mode of action. Biometals. 2016;**29**:39-52. DOI: 10.1007/s10534-015-9894-0

[60] Wang H-L, Yang Z-Y, Wang B. Synthesis, characterization and the antioxidative activity of copper(II), zinc(II) and nickel(II) complexes with naringenin. Transition Metal Chemistry. 2006;**31**:470-474. DOI: 10.1007/s11243-006-0015-3

[61] Pereira RMS, Andrades NED, Paulino N, Sawaya ACHF, Eberlin MN, Marcucci MC, Favero GM, Novak EM, Bydlowski SP. Synthesis and characterization of a metal complex containing naringin and Cu, and its antioxidant, antimicrobial, antiinflammatory and tumor cell cytotoxicity. Molecules. 2007;**12**:1352-1366. DOI: 10.3390/12071352

[62] Etcheverry SB, Ferrer EG, Naso L, Rivadeneira J, Salinas V, Williams PA. Antioxidant effects of the VO(IV) hesperidin complex and its role in cancer chemoprevention. Journal of Biological Inorganic Chemistry. 2008;**13**:435-447. DOI: 10.1007/s00775-007-0332-9

[63] Dowling S, Regan F, Hughes H. The characterisation of structural and antioxidant properties of isoflavone metal chelates. Journal of Inorganic Biochemistry. 2010;**104**:1091-1098. DOI: 10.1016/j.jinorgbio.2010.06.007

[64] López-Lázaro M, Willmore E, Austin CA. The dietary flavonoids myricetin and fisetin act as dual inhibitors of DNA topoisomerases I and II in cells. Mutation Research/ Genetic Toxicology and Environmental Mutagenesis. 2010;**696**:41-47. DOI: 10.1016/j.mrgentox.2009.12.010

[65] Casagrande F, Darbon JM. Effects of structurally related flavonoids on cell cycle progression of human melanoma cells: Regulation of cyclin-dependent kinases CDK2 and CDK1. Biochemical Pharmacology. 2001;**61**:1205-1215. DOI: 10.1016/S0006-2952(01)00583-4

[66] Khan N, Asim M, Afaq F, Abu Zaid M, Mukhtar H. A novel dietary flavonoid fisetin inhibits androgen receptor signaling and tumor growth in athymic nude mice. Cancer Research. 2008;**68:**8555-8563. DOI: 10.1158/0008-5472

[67] Bohl M, Tietze S, Sokoll A, Madathil S, Pfennig F, Apostolakis J, Fahmy K, Gutzeit HO. Flavonoids affect actin functions in cytoplasm and nucleus. Biophysical Journal. 2007;**93**:2767-2780. DOI:10.1529/biophysj.107.107813

[68] Sinha S, Amin H, Nayak D, Bhatnagar M, Kacker P, Chakraborty S, Ghosal S. Assessment of microtubule depolymerization property of flavonoids isolated from *Tanacetum gracile* in breast cancer cells by biochemical and molecular docking approach. Chemico-Biological Interactions. 2015;**239**:1-11. DOI: 10.1016/j.cbi.2015.06.034

[69] Erdogan S, Doganlar O, Doganlar ZB, Serttas R, Turkekul K, Dibirdik I, Bilir A. The flavonoid apigenin reduces prostate cancer CD44+ stem cell survival and migration through PI3K/Akt/NF-κB signaling. Life Sciences. 2016;**162**:77-86. DOI: 10.1016/j.lfs.2016.08.019

[70] Tan M, Zhu J, Pan Y, Chen Z, Liang H, Liu H, Wang H. Synthesis, cytotoxic activity, and DNA binding properties of copper (II) complexes with hesperetin, naringenin, and apigenin. Bioinorganic Chemistry and Applications. 2009;Article ID 347872, 9 pages. DOI: 10.1155/2009/347872

[71] Durgo K, Halec I, Sola I, Franekic J. Cytotoxic and genotoxic effects of the quercetin/ lanthanum complex on human cervical carcinoma cells in vitro. Archives of Industrial Hygiene and Toxicology. 2011;**62**:221-227. DOI: 10.2478/10004-1254-62-2011-2122

[72] Kasprzak MM, Erxleben A, Ochocki J. Properties and applications of flavonoid metal complexes. RSC Advances. 2015;**5**:45853-45877. DOI: 10.1039/C5RA05069C

[73] Chen X, Tang LJ, Sun YN, Qiu PH, Liang G. Syntheses, characterization and antitumor activities of transition metal complexes with isoflavone. Journal of Inorganic Biochemistry. 2010;**104**:379-384. DOI: 10.1016/j.jinorgbio.2009.11.008

[74] Andrades Ikeda NE, Novak EM, Maria DA, Velosa AS, Pereira RM. Synthesis, characterization and biological evaluation of Rutin-zinc(II) flavonoid -metal complex. Chemico-Biological Interactions. 2015;**239**:184-191. DOI: 10.1016/j.cbi.2015.06.011

[75] Naso LG, Lezama L, Valcarcel M, Salado C, Villacé P, Kortazar D, Ferrer EG, Williams PA. Bovine serum albumin binding, antioxidant and anticancer properties of an oxidovanadium(IV) complex with luteolin. Journal of Inorganic Biochemistry 2016;**157:**80-93. DOI: 10.1016/j.jinorgbio.2016.01.021

[76] Islas MS, Naso LG, Lezama L, Valcarcel M, Salado C, Roura-Ferrer M, Ferrer EG, Williams PA. Insights into the mechanisms underlying the antitumor activity of an oxidovanadium (IV) compound with the antioxidant naringenin. Albumin binding studies. Journal of Inorganic Biochemistry. 2015;**149**:12-24. DOI: 10.1016/j.jinorgbio.2015.04.011

[77] León IE, Cadavid-Vargas JF, Resasco A, Maschi F, Ayala MA, Carbone C, Etcheverry S B. *In vitro* and *in vivo* antitumor effects of the VO-chrysin complex on a new three-dimensional osteosarcoma spheroids model and a xenograft tumor in mice. Journal of Biological Inorganic Chemistry. 2016;**21**:1009-1020. DOI: 10.1007/s00775-016-1397-0

[78] Ferrer EG, Salinas MV, Correa MJ, Naso L, Barrio DA, Etcheverry SB, Lezama L, Rojo T, Williams PA. Synthesis, characterization, antitumoral and osteogenic activities of quercetin vanadyl(IV) complexes. Journal of Biological Inorganic Chemistry. 2006;**11**:791-801. DOI: 10.1007/s00775-006-0122-9

[79] Dell'Anna MM, Censi V, Carrozzini B, Caliandro R, Denora N, Franco M, Veclani D, Melchior A, Tolazzi M, Mastrorilli P. Triphenylphosphane Pt(II) complexes containing biologically active natural polyphenols: Synthesis, crystal structure, molecular modeling and cytotoxic studies. Journal of Inorganic Biochemistry. 2016;**163**:346-361. DOI: 10.1016/j.jinorgbio.2016.08.006

[80] Kasprzak M, Fabijańska M, Chęcińska L, Studzian K, Markowicz-Piasecka M, Sikora J, Mikiciuk-Olasik E, Ochocki J. Small differences in structure, a large difference in activity—Comparing a new Ru(II)-3-hydroxyiminoflavanone complex with analogous Ru(II) compounds. Inorganica Chimica Acta. 2016;**457**:69-80. DOI: 10.1016/j.ica.2016.11.021

[81] Kurzwernhart A, Kandioller W, Bächler S, Bartel C, Martic S, Buczkowska M, Mühlgassner G, Jakupec MA, Kraatz HB, Bednarski PJ, Arion VB, Marko D, Keppler BK, Hartinger CG. Structure-activity relationships of targeted RuII(η^6-p-Cymene) anticancer complexes with flavonol-derived ligands. Journal of Medicinal Chemistry. 2012;**55**: 10512-10522. DOI: 10.1021/jm301376a

[82] Tan J, Zhu L, Wang B. DNA binding, cytotoxicity, apoptotic inducing activity, and molecular modeling study of quercetin zinc(II) complex. Bioorganic Medicinal Chemistry. 2009;**17**:614-620. DOI: 10.1016/j.bmc.2008.11.063

[83] Tan J, Zhu L, Wang B. GC (Guanine-cytosine)-selective DNA-binding and antitumor activity of a quercetin-manganese (II) complex. Chemistry & Biodiversity. 2011;**8**:1550-1559. DOI: 10.1002/cbdv.201000313

[84] Spoerlein C, Mahal K, Schmidt H, Schobert R. Effects of chrysin, apigenin, genistein and their homoleptic copper(II) complexes on the growth and metastatic potential of cancer cells. Journal of Inorganic Biochemistry. 2013;**127**:107-115. DOI: 10.1016/j.jinorgbio.2013.07.038

[85] Parveen S, Tabassum S, Arjmand F. Human topoisomerase I mediated cytotoxicity profile of l-valine-quercetin diorganotin(IV) antitumor drug entities. Journal of Organometallic Chemistry. 2016;**823**:23-33. DOI: 10.1016/j.jorganchem.2016.09.015

[86] Lara PNJ, Douillard J-Y, Nakagawa K, von Pawel J, McKeage MJ, Albert I, Losonczy G, Reck M, Heo DS, Fan X, Fandi A, Scagliotti G. Randomized phase III placebo-controlled trial of carboplatin and paclitaxel with or without the vascular disrupting agent vadimezan (ASA404) in advanced non-small-cell lung cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2011;**29**:2965-2971. DOI: 10.1200/JCO.2011.35.0660

[87] Abou-Zied OK, Al-Shihi OI. Characterization of subdomain IIA binding site of human serum albumin in its native, unfolded, and refolded states using small molecular probes. Journal of American Chemical Society. 2008;**130**:10793-801. DOI: 10.1021/ja8031289

[88] Sarzehi S, Chamani J. Investigation on the interaction between tamoxifen and human holo-transferrin: Determination of the binding mechanism by fluorescence quenching, resonance light scattering and circular dichroism methods. International Journal of Biological Macromolecules. 2010;**47**:558-569. DOI: 10.1016/j.ijbiomac.2010.08.002

[89] Zhang XF, Han RM, Sun XR, Li GY, Yang QF, Li Q, Gai W, Zhang M, Chen L, Yang G, Tang YL. The effect of the skeleton structure of flavanone and flavonoid on interaction with transferrin. Bioorganic & Medicinal Chemistry Letters. 2013;**23**:6677-6681. DOI: 10.1016/j.bmcl.2013.10.042

[90] Nitiss JL. Targeting DNA topoisomerase II in cancer chemotherapy. Nature reviews Cancer. 2009;**9**:338-350. doi:10.1038/nrc2607.

[91] Sanna D, Ugone V, Pisano L, Serra M, Micera G, Garribba E. Behavior of the potential antitumor $V^{IV}O$ complexes formed by flavonoid ligands. 2. Characterization of sulfonate derivatives of quercetin and morin, interaction with the bioligands of the plasma and preliminary biotransformation studies. Journal of Inorganic Biochemistry. 2015;**153**:167-177. DOI: 10.1016/j.jinorgbio.2015.07.018

[92] Wang J, Wang Q, Wu D, Yan J, Wu Y, Li H. Comparative studies on the interactions of baicalein and Al(III)-baicalein complex with human serum albumin. Luminescence 2016;**31**:54-62. DOI: 10.1002/bio.2921

[93] Guo Q, Yuan J, Zeng J. Binding of dihydromyricetin and its metal ion complexes with bovine serum albumin. Biotechnology & Biotechnological Equipment. 2014;**28**:333-341. DOI: 10.1080/13102818.2014.915077

[94] Liu E, Zhang H. Interaction of the La(III)–morin complex with human serum albumin. Journal of Solution Chemistry. 2014;**43**:1402-1413. DOI: 10.1007/s10953-014-0210-3

[95] Kurzwernhart A, Kandioller W, Bartel C, Bächler S, Trondl R, Mühlgassner G, Jakupec MA, Arion VB, Marko D, Keppler BK, Hartinger CG. Targeting the DNA-topoisomerase complex in a double-strike approach with a topoisomerase inhibiting moiety and covalent DNA binder. Chemical Communications.2012;48:4839-4841. DOI: 10.1039/C2CC31040F

[96] Tabassum S, Zaki M, Afzal M, Arjmand F. New modulated design and synthesis of quercetin-Cu(II)/Zn(II)-Sn_2(IV) scaffold as anticancer agents: in vitro DNA binding profile, DNA cleavage pathway and Topo-I activity. Dalton Transactions. 2013;**42**:10029-10041. DOI: 10.1039/c3dt50646k

[97] Kang J, Zhuo L, Lu X, Liu H, Zhang M, Wu H. Electrochemical investigation on interaction between DNA with quercetin and Eu-Qu3 complex. Journal of Inorganic Biochemistry. 2004;**98**:79-86. DOI: 10.1016/j.jinorgbio.2003.08.015

[98] Jamali AA, Tavakoli A, Nazhad Dolatabadi JE. Analytical overview of DNA interaction with Morin and its metal complexes. European Food Research and Technology. 2012 **235**:367-373. DOI: 10.1007/s00217-012-1778-8

[99] Selvaraj S, Krishnaswamy S, Devashya V, Sethuraman S, Krishnan UM. Flavonoid-metal ion complexes: a novel class of therapeutic agents. Medicinal Research Reviews, 2014;**34**:677-702. DOI: 10.1002/med.21301

[100] Li J, Kang J, Lu J, Li X, Tang J, Zhang H, Zhang Y. Determination of calf thymus DNA using resonance light-scattering quenching method based on the terbium (III) (Tb^{3+})/ europium (III) (Eu^{3+})–quercetin system. Journal of Luminescence. 2009;**129**:906-911. DOI: 10.1016/j.jlumin.2009.03.015

[101] El Amrani FB, Perelló L, Real JA, González-Alvarez M, Alzuet G, Borrás J, García-Granda S, Montejo-Bernardo J. Oxidative DNA cleavage induced by an iron(III) flavonoid complex: Synthesis, crystal structure and characterization of chlorobis(flavonolato) (methanol) iron(III) complex. Journal of Inorganic Biochemistry. 2006;100:1208-1218. DOI: 10.1016/j.jinorgbio.2006.01.036

[102] Niu S, Wu M, Bi S, Zhang S. Reaction of Cd(II)-Morin with dsDNA for biosensing of ssDNA oligomers with complementary, GCE-immobilized ssDNA. Bioelectrochemistry. 2008;73:64-69. DOI: 10.1016/j.bioelechem.2008.04.021

[103] Song Y, Yang P, Yang M, Kang J, Qin S, Lü B, Wang L. Spectroscopic and voltammetric studies of the cobalt (II) complex of Morin bound to calf thymus DNA. Transition Metal Chemistry. 2003;28:712-716. DOI: 10.1023/A:1025418332121

[104] Temerk YM, Ibrahim MS, Kotb M. Voltammetric and spectroscopic studies on binding of antitumor Morin, Morin-Cu complex and Morin-β-cyclodextrin with DNA. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2009;71:1830-1836. DOI: 10.1016/j.saa.2008.07.001

[105] Niu SY, Wu ML, Hu LZ, Mei ZH, Liu SF. Nucleic acid biosensor for DNA hybridization detection using rutin-Cu as an electrochemical indicator. Electrochimica Acta. 2009;54:1564-1569. DOI: 10.1016/j.electacta.2008.09.038

[106] Ni Y, Du S, Kokot S. Interaction between quercetin-copper(II) complex and DNA with the use of the neutral red dye fluorophore probe. Analytica Chimica Acta, 2007;584:19-27. DOI: 10.1016/j.aca.2006.11.006

[107] Zeng YB, Yang N, Liu WS, Tang N. Synthesis, characterization and DNA-binding properties of La(III) complex of chrysin. Journal of Inorganic Biochemistry. 2003;97:258-264. DOI: 10.1016/S0162-0134(03)00313-1

[108] Tan J, Wang B, Zhu L (). Hydrolytic cleavage of DNA by quercetin zinc(II) complex. Bioorganic and Medicinal Chemistry Letters. 2007;17:1197-1199. DOI: 10.1016/j.bmcl.2006.12.023

[109] Rusak G, Piantanida I, Bretschneider S, Ludwig-Muller J. Complex formation of quercetin with lanthanum enhances binding to plant viral satellite double stranded RNA. Journal of Inorganic Biochemistry. 2009;103:1597-1601. DOI: 10.1016/j.jinorgbio.2009.08.008

[110] Marinic M, Piantanida I, Rusak G, Zinic M. Interactions of quercetin and its lanthane complex with double stranded DNA/RNA and single stranded RNA: Spectrophotometric sensing of poly G. Journal of Inorganic Biochemistry. 2006;100:288-298. DOI: 10.1016/j.jinorgbio.2005.11.013

[111] Tan J, Zhu L, Wang B. From GC-rich DNA binding to the repression of survivin gene for quercetin nickel (II) complex: Implications for cancer therapy. Biometals. 2010;23:1075-1084. DOI: 10.1007/s10534-010-9353-x

[112] Al-Amiery AA, Kadhum AAH, Mohamad AB. Antifungal and antioxidant activities of pyrrolidone thiosemicarbazone complexes. Bioinorganic Chemistry and Applications. 2012; Article ID 795812, 6 pages. DOI:10.1155/2012/795812

[113] Tarahovsky YS, Yagolnik EA, Muzafarov EN, Abdrasilov BS, Kim YA. Calcium-dependent aggregation and fusion of phosphatidylcholine liposomes induced by complexes of flavonoids with divalent iron. Biochimica et Biophysica Acta. 2012;1818:695-702. DOI:10.1016/j.bbamem.2011.12.001

[114] Kim YA, Tarahovsky YS, Yagolnik EA, Kuznetsova SM, Muzafarov EN. Lipophilicity of flavonoid complexes with iron(II) and their interaction with liposomes. Biochemical and Biophysical Research Communications. 2013;431:680-685. DOI: 10.1016/j.bbrc.2013.01.060

[115] Kim YA, Tarahovsky YS, Yagolnik EA, Kuznetsova S. Integration of quercetin-Iron complexes into phosphatidylcholine or phosphatidylethanolamine liposomes. Applied Biochemistry and Biotechnology. 2015;176:1904-1913. DOI: 10.1007/s12010-015-1686-z

[116] Jabeen E, Janjua NK, Hameed S. β-Cyclodextrin assisted solubilization of Cu and Cr complexes of flavonoids in aqueous medium: A DNA-interaction study. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2014;128:191-196. DOI: 10.1016/j.saa.2014.02.132

[117] Gan PP, Li SFY. Potential of plant as a biological factory to synthesize gold and silver nanoparticles and their applications. Reviews in Environmental Science and Biotechnology. 2012;11:169-206. DOI: 10.1007/s11157-012-9278-7

[118] Voicescu M, Craciunescu O, Moldovan L, Anastasescu M, Angelescu DG, Teodorescu VS. Physicochemical characterization and in vitro cytotoxic effect of 3-hydroxyflavone in a silver nanoparticles complex. Journal of Fluorescence. 2015;25:1215-1223. DOI: 10.1007/s10895-015-1608-z

[119] Yue H-L, Hu Y-J, Huang H-G, Jiang S, Tu B. Development of morin-conjugated Au nanoparticles: Exploring the interaction efficiency with BSA using spectroscopic methods. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2014;**130**:402-410. DOI: 10.1016/j.saa.2014.04.022

[120] Kumar SR, Priyatharshni S, Babu VN, Mangalaraj D, Viswanathan C, Kannan S, Ponpandian N. Quercetin conjugated superparamagnetic magnetite nanoparticles for in-vitro analysis of breast cancer cell lines for chemotherapy applications. Journal of Colloid and Interface Science. 2014;436:234-242. DOI: 10.1016/j.jcis.2014.08.064

[121] Barreto ACH, Santiago VR, Mazzetto SE, Denardin JC, Lavín R, Mele G, Ribeiro MENP, Vieira IGP, Gonçalves T, Ricardo NMPS, Fechine PBA. Magnetic nanoparticles for a new drug delivery system to control quercetin releasing for cancer chemotherapy. Journal of Nanoparticles Research. 2011;13:6545-6553. DOI: 10.1007/s11051-011-0559-9

[122] Horcajada P, Ramila A, Ferey G, Vallet-Regí M. Influence of superficial organic modification on MCM-41 matrices on drug delivery rate. Solid State Sciences. 2006;8:1243-1249. DOI: 10.1016/j.solidstatesciences.2006.04.016

[123] Popova M, Trendafilova I, Szegedi A, Mihály J, Németh P, Marinova SG, Aleksandrov HA, Vayssilov GN. Experimental and theoretical study of quercetin complexes formed on pure silica and Zn-modified mesoporous MCM-41 and SBA-16 materials. Microporous and Mesoporous Materials. 2016;228:256-265. DOI: 10.1016/j.micromeso.2016.04.001

[124] Tomečkova V, Rehakova M, Mojžišova G, Magura J, Wadsten T, Zelenakova K. Modified natural clinoptilolite with quercetin and quercetin dihydrate and the study of their anticancer activity. Microporous and Mesoporous Materials. 2012;**147**:59-67. DOI: 10.1016/j.micromeso.2011.05.031

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