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Flavonoid–membrane interactions: Involvement of flavonoid–metal complexes in raft signaling

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ABSTRACT

Flavonoids are polyphenolic compounds produced by plants and delivered to the human body through food. Although the epidemiological analyses of large human populations did not reveal a simple correlation between flavonoid consumption and health, laboratory investigations and clinical trials clearly demonstrate the effectiveness of flavonoids in the prevention of cardiovascular, carcinogenic, neurodegenerative and immune diseases, as well as other diseases. At present, the abilities of flavonoids in the regulation of cell metabolism, gene expression, and protection against oxidative stress are well-known, although certain biophysical aspects of their functioning are not yet clear. Most flavonoids are poorly soluble in water and, similar to lipophilic compounds, have a tendency to accumulate in biological membranes, particularly in lipid rafts, where they can interact with different receptors and signal transducers and influence their functioning through modulation of the lipid-phase behavior. In this study, we discuss the enhancement in the lipophilicity and antioxidative activity of flavonoids after their complexation with transient metal cations. We hypothesize that flavonoid–metal complexes are involved in the formation of molecular assemblies due to the facilitation of membrane adhesion and fusion, protein–protein and protein–membrane binding, and other processes responsible for the regulation of cell metabolism and protection against environmental hazards.

Contents

1. Introduction

Flavonoids are not synthesized in animal cells, and their presence in tissues strictly depends on the intake of plant products. Although

Abbreviations: BSA, bovine serum albumin; DOPC, dioleoylphosphatidylcholine; HSA, human serum albumin; EC, epicatechin; ECG, epicatechin gallate; EGC, epigallocatechin; EGCG, epigallocatechin gallate

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flavonoids were found to exhibit considerable therapeutic potential in laboratory experiments, long-time epidemiological analyses on large human populations did not reveal a simple correlation between flavonoid consumption and a decrease in carcinogenic or cardiovascular diseases [1]. The influence of flavonoids on human health remains unclear. Unlike universally recognized vitamins, the shortage of flavonoids in food does not lead to the development of a pronounced deficiency syndrome; therefore, the original attribution of flavonoids to vitamins, such as vitamin P, was later declined [2].

The attractiveness of flavonoids is based on their positive influence on human health and the therapeutic potential of their synthetic derivatives, including potent anti-inflammatory, anticarcinogenic, antiviral, antiparasitic, and bactericidal chemicals and antibiotics that may reveal higher efficiency than conventional medicines. Moreover, flavonoids and their derivatives may potentiate the action of other drugs by overcoming multidrug resistance [3–6]. It is noteworthy that flavonoids and their chemical derivatives are often less toxic and reveal lower side effects than derivatives produced from other natural compounds. Nevertheless, similar to any chemical, flavonoids can be harmful at high doses. Although the side effects of their intake have not been widely studied [7], high doses of purified flavonoids, which are often suggested by drugstores, should be the subject of concern [8].

Due to the medical use of flavonoids, a considerable increase in studies on their influence on human health has been recently observed. During the last two decades, the number of studies in this area revealed an approximately tenfold increase and now reaches more than 5000 publications a year (Fig. 1). This is approximately equal to the number of studies on drug delivery and twofold higher than the number of studies on gene therapy. Typically, modern studies of medical plants include a thorough analysis of their flavonoid composition as a potentially important therapeutic factor, and the therapeutic potential of plant remedies is often attributed to the presence of some flavonoids. Numerous studies have attempted to improve the therapeutic activity and bioavailability of flavonoids through chemical modification and the use of nanomaterials. Despite extensive recent investigations, the mechanisms of flavonoid action are far from clear. At present, this area of scientific research warrants further investigation, and the general theory of flavonoid therapeutic action remains to be elucidated.

2. Flavonoids as plant polyphenolic compounds

Phenolic molecules consist of one or more aromatic rings bearing one or more hydroxide groups. Flavonoids represent one of the best studied and diverse classes of natural polyphenols that are abundantly present in various plant tissues. The 15-carbon frame of flavonoids consists of two aromatic rings (A and B) connected by three carbon atoms. In general, flavonoids are usually described by the formula $C_6-C_3-C_6$ [9], and their classification is based on differences in the structure of the three carbon atoms connecting the aromatic rings. The distinctive features of this C_3 chain are associated with the presence or absence of the double bond, the choice of carbonyl or carboxyl moiety, and the possibility of forming a penta- or hexagonal ring C (Fig. 2).

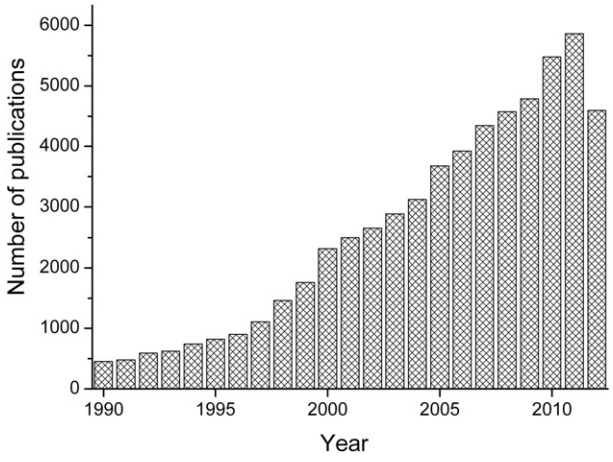

Fig. 1. Number of studies on flavonoids performed in different years according to PubMed (NCBI, MD, USA). The keyword "flavonoids" was used to search the database with the Reference Manager software (ICI ResearchSoft, USA).

In plant tissues, most flavonoids, excluding flavan-3-ols, are represented by both aglycones and various glycosides in which the glycoside part is attached to an oxygen atom that is preferably located in position 3, 7, 3′, or 4′. Glycosides usually bear one or several pyranoside or furanoside carbohydrate residues [10] and may be composed not only of glucose and mannose but also of some rare sugars, such as allose, galacturonic acid, and apiose [11].

It is difficult to determine the main factors responsible for the influence of flavonoids on animal health because these compounds may control numerous processes in the bodies of animals that consume plants as food. First, we have to mention the antioxidative properties of flavonoids [12,13], their ability to influence functions of ATP-dependent protein transporters, including ABC transporters of drugs [14], and their ability to control membrane processes by affecting the fluidity and stability of the phospholipid bilayer of membranes [15–18]. Here, we suggest that the action of flavonoids may be related to an increase in their lipophilicity after complexation with iron cations [19,20], as was recently found.

3. Interaction of flavonoids with the phospholipid bilayer

The lipophilicity of flavonoids and their ability to interact with biological membranes are important factors of their pharmacological activity. Similar to polyphenols, many flavonoids contain a number of hydroxyl groups that impart some polarity and weak acidic properties to the molecules. The inverse correlation between the number of hydroxyl groups and the lipophilicity of flavonoids has been demonstrated experimentally [21]. The interaction with the lipid bilayer depends on the pH, which determines the electrostatic charges of the flavonoid and lipid molecules. According to a general rule, a lower pH results in a lower deprotonation of polar groups and thus a deeper penetration of flavonoids into the lipid bilayer [22]. Although most flavonoids reveal some lipophilicity, their glycosides are considerably more water-soluble [23].

Catechins are the subject of many studies on flavonoid/membrane interactions. Catechins with gallate groups (ECG and EGCG) are better adsorbed by the lipid bilayer than gallate-free catechins (EC and EGC). The revealed affinity of catechins to the lipid bilayer decreases in the order ECG > EGCG > EC > EGC [24–27], which correlates with their lipophilicity based on the octanol:water partition coefficient [24]. After adsorption to the bilayer surface, all catechins penetrate into a region located under phosphate groups and laterally diffuse into the bilayer plane. Molecular modeling reveals that each molecule of EGCG may interact with 10.8 lipid molecules, which results in a 0.374-nm^2 increase in the bilayer surface [28]. Catechins are unevenly distributed in the bilayer plane and reveal a tendency to produce aggregates, as can be observed both in molecular models [29] and in experiments with liposomes [25]. The heterogeneity of the bilayer leads to the formation of defects and increases the permeability of liposomes [30]. NMR studies have revealed that flavonoids in the lipid bilayer do not penetrate deeply into the hydrophobic region and are located closer to the phosphate groups, whereas the galloyl groups of ECG and EGCG are found in the vicinity of the trimethylammonium groups of phosphatidylcholine [31,32]. Moreover, NMR was used to detect the interaction between the positively charged quarterly ammonium of phosphatidylcholine and the π-electrons of galloyl groups (cation–π interaction). According to Uekusa and colleagues, the cation–π interaction may participate in the stabilization of catechin molecules in the interphase region of the phospholipid bilayer [31]. In addition, NMR was used to reveal that

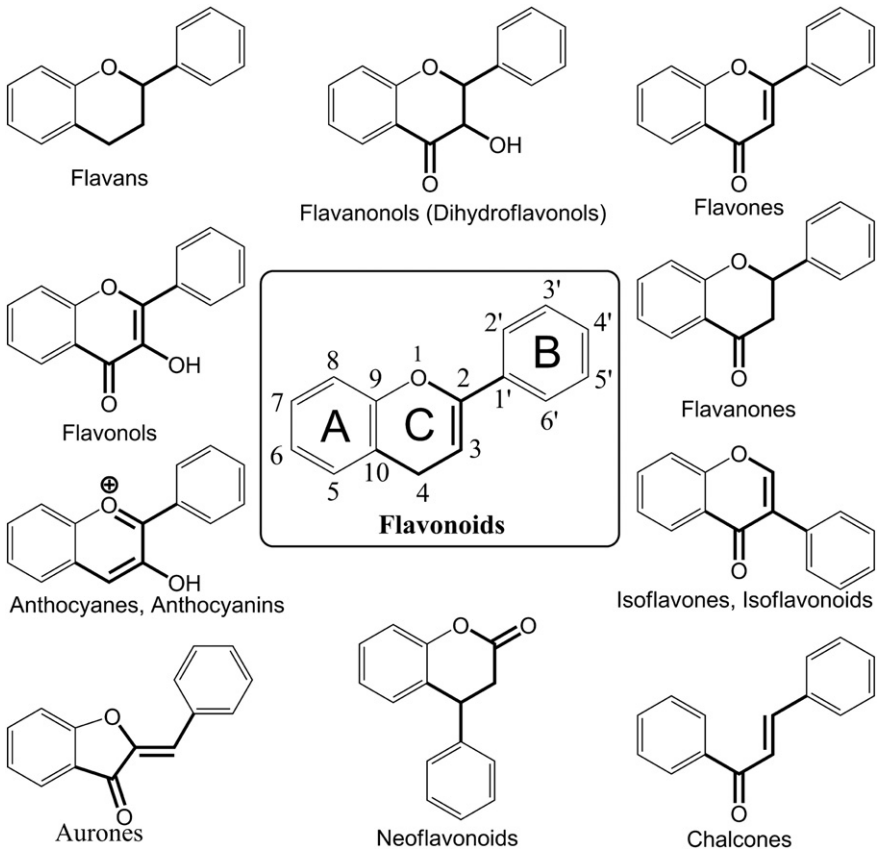

Fig. 2. Classification of flavonoids based on the structure of the C2 – C4 carbon chain (highlighted in bold). An example of the typical enumeration of carbon atoms is presented in the center.

the rotation axis of catechin is 55° tilted toward the bilayer plane [31], whereas the distance between the lipid phosphate and the catechin carbonyl is equal to 5.3 ± 0.1 Å.

The ability of flavonoids to interact with the polar/nonpolar regions of the lipid bilayer was demonstrated by various experimental approaches. X-ray scattering and molecular simulations revealed that the flavonoids quercetin, genistein, and daidzein are mainly located close to the polar area of the bilayer in the region composed of the phosphate and carbonyl groups of fatty acids. The long axes of flavonoids are preferably parallel, whereas the planes of rings are perpendicular to the bilayer plane [33,34]. Some flavonoids exhibit two-color fluorescence behavior and can serve as sensitive fluorescent probes for non-invasive studies of their interaction with the hydrophobic core and the polar regions of the phospholipid bilayer [35]. It has been found that polyphenol molecules, including flavonoids, are incorporated into a relatively hydrophobic fatty acid chain region, where they are well shielded from water [36]. The phototautomeric behavior of 3-hydroxyflavone makes it possible to reveal that one fraction of this flavonoid is located in the inner hydrophobic core, whereas the other one resides near the water-accessible surface [37]. Fluorescent spectroscopy studies revealed that 15% of the flavonoid daidzein is located in the hydrophobic region of the membrane and that the rest is distributed in the aqueous bulk and the aqueous/membrane interface [38]. Fluorescence and EPR spectroscopy techniques demonstrated that the flavonoid genistein is preferentially intercalated in the phospholipid headgroup region, to some extent in the polar–apolar interface, and to a minimal extent in the hydrophobic core of the membrane [39]. Genistein provokes a significant increase in the membrane order parameter (which is reciprocally proportional to the membrane fluidity), whereas no similar effects were observed for daidzein. Accordingly, it was suggested that genistein may exert its anti-metastatic effects by changing the mechanical properties of prostate cancer cells, whereas daidzein should be applied at higher concentrations than genistein to achieve pharmacological effects [16]. According to data obtained using the FTIR, ^{1}H NMR, and EPR techniques, the flavonoid apigenin incorporates into the bilayer of DPPC liposomes via overcoming the hydrogen bonding between its own hydroxyl groups and the lipid polar head groups in the COPOC segment. It has been hypothesized that the hydroxyl groups of apigenin link with the polar groups of DPPC by water bridges. This flavonoid may exert a strong rigidifying effect on polar head groups [40].

4. Penetration of flavonoids through membranes of the intestinal epithelium

The daily consumption of flavonoids depends on the diet and varies from tenths of milligrams to a few grams [1,41]. In the intestinal lumen, flavonoid-O-glycosides are attacked by hydrolases exhibiting multiple enzymatic activities, which results in the release of flavonoid aglycones. The aglycones are delivered to the human body through the membranes of the intestinal epithelium, which covers more than 90% of the intestinal surface [42]. The bioavailability of flavonoids is very low. Less than 1% of the consumed flavonoids enter the blood [43].

The hydrolysis of flavonoid glycosides by β-glucosidase and the subsequent attachment of glucuronic acid occur after the penetration of the glycosides into the cytoplasm of enterocytes, which are the cells of the intestinal epithelium [44]. Furthermore, the portal vein transports these substances to the liver, where they are methylated and sulfated with appropriate transferases [45]. Thus, in the blood, only 5–10% of the flavonoids are not modified [46], whereas glucuronides are predominant [47].

Among the foodstuffs that are consumed daily, tea contains the largest amount of flavonoids. First, we should mention that green tea contains up to 30% catechins, as calculated based on the weight of dry leaves [48]. Two hours after the consumption of one cup of green or

black tea, the blood plasma contains 0.3–1.0 μM catechins. At higher doses, the concentration of catechins can reach 10 μM [49–51]. The bioavailability of quercetin, naringenin, or hesperidin is lower than that of catechins, but their concentration in blood can also reach tens or hundreds of nanomoles per liter when large amounts of fruits and vegetables are consumed [52].

The mechanism through which flavonoids overcome the hydrophobic barrier of cell membranes remains to be fully elucidated. It is well known that flavonoid aglycones are only slightly soluble in water and sufficiently lipophilic for spontaneous penetration through the lipid bilayer. Although flavonoids are preferably found in the periphery of the lipid bilayer, the probability of their presence at the center of the bilayer is not zero, as calculated from the free energy profile, which allows a flavonoid molecule to spontaneously cross the bilayer [33].

Water-soluble glucosides of flavonoids, such as quercetin monoglucosides, but not diglucosides can pass over epithelium membranes via the glucose transporters GLUT-1 [53,54] and GLUT2 [55]. The transporter-dependent translocation of quercetin glucosides was found to be more efficient than the spontaneous penetration of quercetin aglycones through the lipid bilayer [44]. Moreover, the main insulin-regulated glucose transporter GLUT4 may also participate in the translocation of hydrophobic flavonoid aglycones [56]. It is interesting that the flavonoid genistein can inhibit this transporter, thereby regulating the insulin-dependent glucose transport in adipocytes [57]. Similarly, the flavonoids naringenin [58] and phlorizin [59] can decrease the adsorption of sugars by the intestinal epithelium, which could be useful in diabetes treatment. The bilirubin transporter bilitranslocase is also involved in the transport of flavonoids in gastrointestinal [60] and endothelial cells [61]. In contrast, flavonoids can inhibit the monocarboxylate transporters MST2 and SLC-16, which are responsible for the translocation of lactates, pyruvates, ketone bodies [62], and various drugs [63]; however, to the best of our knowledge, the involvement of these transporters in flavonoid translocation has not been studied.

5. Lipid rafts and caveolae

Cell membranes represent a complex mosaic structure. The nonrandom distribution of lipids as a result of molecular segregation and the formation of domains can be observed even on artificial bilayers composed of lipids with different melting temperatures [64]. The formation of molecular domains may lead to variations in the compositions of neighboring areas of the bilayer [64,65]. One of the most studied mosaic structures, which are known as lipid rafts, was initially found in apical membranes of epithelial cells enriched with sphingomyelin and cholesterol [66], and numerous studies on lipid rafts were then performed on different cells. It was detected that lipid rafts are located on the external leaflet of the plasma membrane and consist of tightly packed domains of cholesterol and saturated sphingomyelin that float in a lake of melted and loosely packed unsaturated lipids. The final definition of rafts as "small (10–200 nm), heterogeneous, highly dynamic, sterol- and sphingolipid-enriched domains that compartmentalize cellular processes" was presented on a Keystone Symposium in 2006 [67].

It was found that rafts participate in various biological processes, including the viral [68,69], bacterial [70], parasitic [71], and fungal infection of cells [72]. Moreover, rafts are involved in apoptosis, immune response, cell signaling, and communication processes [73]. Disturbances in cell signaling processes in lipid rafts result in various membrane-related dysfunctions [74], including inflammation [75], immune disorders [76,77], pathology of liver [78] and of cardiovascular systems [79], atherosclerosis [80], and neuronal degeneration [81].

Rafts are rich in various proteins. For example, the glycophosphatidylinositol-anchored protein (GPI-AP) is able to diffuse laterally in rafts and produce dimers with cholesterol [82]. Moreover, proteins covalently attached to palmitic acid [83] or covalently attached to cholesterol [84] also have a tendency to accumulate in rafts (Fig. 3). The proteins present in rafts, such as receptors [85] and channel

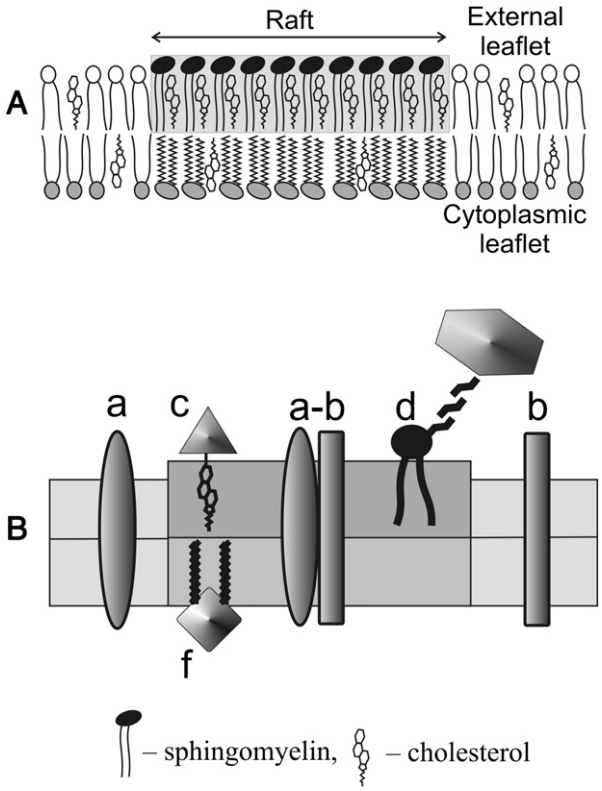

Fig. 3. Structure of rafts. (A) Sphingomyelin and cholesterol packing in a raft located on the external leaflet of the plasma membrane. It is hypothesized that the cytoplasmic leaflet of the membrane is also modified in the area apposed to the raft. (B) Organization of proteins in the raft (the same fragment of the plasma membrane is presented). Transmembrane proteins (a) and (b) enter the raft and produce a functionally active complex (a–b). Peripheral proteins attached to cholesterol (c) or glycophospholipids (d) are also present in the raft. After palmitoylation, some proteins can be recruited in the area apposed to the raft on the cytoplasmic leaflet (f).

proteins [86], may participate in cell regulatory processes. For example, the Hedgehog protein (Hh) attached to the membrane through palmitoylation or cholesterinization [87] accumulates in rafts and participates in cell signaling during embryogenesis [88,89]. It was found that a similar raft protein, namely Sonic Hedgehog (SHh), can be used as a target for the therapeutic treatment of damaged brain tissues [90], different cancers [91–95], and cardiovascular disorders [96]. The tumor necrosis factor receptor (TNFR), which is responsible for apoptosis, is also accumulated in rafts and can be used for the treatment of cancer cells [97].

Some rafts are involved in the processes of caveolar endocytosis. Caveolae are regarded as a special group of rafts present in the plasma membrane of different cells, including endothelium, smooth muscles, fibroblasts, and adipocytes [98–100]. Similar to other rafts, caveolae are rich in cholesterol and sphingomyelin and also contain caveolin proteins responsible for plasma membrane invaginations during endocytosis (Fig. 4) [101].

6. Delivery of flavonoids to lipid rafts

When present in blood, flavonoids interact with different water-soluble proteins, particularly albumins. This interaction was described in studies of kaempferol, galangin, diosmetin [102], luteolin, taxifolin, catechins [103], and other flavonoids. The interaction of dihydrochalcone with bovine serum albumin (BSA) was found to be spontaneous, controlled by hydrophobic forces, and accompanied with a release of energy [104]. The spontaneous interaction with site II of subdomain IIIA of BSA was described for morin [105], whereas apigenin interacts with site I of subdomain II of BSA [106]. A similar site of human serum albumin

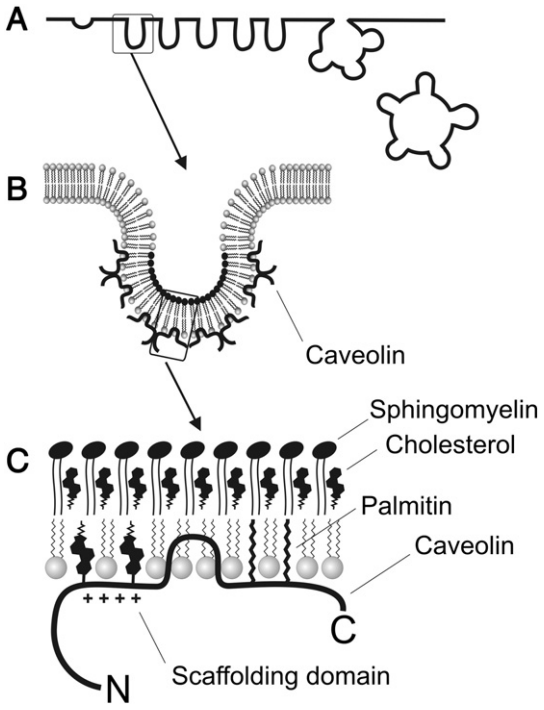

Fig. 4. Schematic representation of a caveolae structure. (A) On the plasma membrane, caveolae appear as numerous invaginations with a diameter of 60–80 nm that can enter the cytoplasm during endocytosis. (B) Caveolin molecules are attached to the cytoplasmic surface of caveolae. (C) The external leaflet of the caveolar membrane contains cholesterol and sphingomyelin, similar to other rafts. Caveolin has a hydrophobic domain that enters the cytoplasmic leaflet of the bilayer. Moreover, this protein is covalently attached to the bilayer through cholesterol and palmitin. The former is located on the positively charged caveolin site known as the scaffolding domain.

(HSA) was occupied by fisetin [107]. The binding constant of hesperetin to HSA was $1.941 \times 10^4\ M^{-1}$ [108], and the binding constant of the interaction of EC with site II of subdomain IIIA of BSA was $10^6\ M^{-1}$, whereas the binding constant of EGCG with site I of subdomain IIA of BSA was $6.6 \times 10^7\ M^{-1}$. It was hypothesized that the reported difference in the binding of catechins can be attributed to the influence of galloid groups [109].

Flavonoids can also interact with lipoproteins present in blood. Thus, quercetin interacts with low-density lipoproteins (LDL). A protective effect of quercetin against the toxic and apoptotic influences of oxidized LDL was demonstrated on macrophages [110]. A similar protective effect against oxidative stress was observed with delphinidin-3-glucoside adsorbed on LDL [111].

The albumins and lipoproteins of blood are delivered to rafts present on the plasma membrane of different cells and enter the cytoplasm through caveolin-dependent endocytosis. There is considerable evidence for the involvement of caveolae in the endocytosis and transcytosis of LDL and albumins [110,112,113]. We hypothesize that flavonoids can be delivered to rafts with LDL and albumins and that the presence of these compounds in fact may influence the functioning of some regulatory systems. A number of remarkable suggestions regarding the regulatory properties of flavonoids in rafts were recently presented.

7. Influence of flavonoids on rafts and caveolae

The ability of flavonoids to interact with membrane rafts and caveolae has been studied in many laboratories. It has been found that green tea EGCG can influence cell signaling and attenuate inflammatory processes in endothelium cells by decreasing the expression of caveolin-1 and cyclooxygenase COX-2 and inhibiting the ERK 1/2 and Akt kinases of the MAPK signaling pathway [114]. A similar ability to decrease caveolin-1 expression and activate signaling through PI3K and Akt kinases, which are responsible for the regulation of apoptosis and carcinogenesis, was also found in studies of the flavonoid daidzein [115].

In cerebral ischemia, the elevated permeability of the blood brain barrier (BBB) is a characteristic feature of the injured area. It has been demonstrated that green tea polyphenols may decrease the BBB permeability and thus lead to considerable amelioration of the damaged tissues. The observed changes in the permeability correlate with the downregulation of the expression of caveolin-1 in endothelial cells responsible for BBB integrity. In addition, an increase in the expression and phosphorylation of raft ERK1/2 kinases responsible for cell proliferation has also been observed [116].

In endothelial cells, the downregulation of caveolin-1 expression by green tea polyphenols may protect the aorta against the pathological changes induced by a high-fat diet. It is well known that caveolin-1 is a negative regulator of nitric oxide synthase (eNOS). A high-fat diet upregulates the aortic caveolin-1 expression, whereas green tea polyphenols normalize the level of this protein and subsequently the nitric oxide concentration responsible for autoimmune and inflammatory processes. The observed regulation of caveolin-1 expression is controlled by the protein kinases ERK1/2 and p38 MAPK, which are also present in rafts [117].

The glycoprotein laminin belongs to a family of scaffolding proteins that are present in most tissues. Cancer cells reveal elevated amounts of laminin receptors in plasma membrane rafts, which results in tumor metastasis. Green tea EGCG may prevent carcinogenesis by blocking the interaction of epithelium growth factor (EGF) with the corresponding receptor (EGFR) present in rafts [118]. As was demonstrated in a study of multiple myeloma, EGCG can initiate the apoptosis of cancer cells without adversely affecting normal cells. The apoptotic activity of EGCG is explained by its ability to initiate the accumulation of the laminin receptor in lipid rafts of multiple myeloma cells but not in normal blood mononuclear cells. Moreover, EGCG induces the phosphorylation of protein kinase C (PKC) and the translocation of acid sphingomyelinase to the plasma membrane, which results in the apoptosis of myeloma cells [119]. A similar clustering of raft proteins in the presence of EGCG or green tea extract was found in human colon adenocarcinoma COLO 204 cells, but surprisingly, this process leads to the upregulation of cancer cell viability through the MEK/ERK1/2 signaling pathway [120].

The protective antiatherosclerotic effect of green tea catechins is explained by their anti-inflammatory influence on vascular endothelial cells. The induction and compartmentalization of the heme oxygenase-1 enzyme in lipid rafts and caveolae play an important protective role against atherosclerosis. It has been found that EGCG initiates caveolin displacement from the inner surface of the membrane toward the cytoplasm. Moreover, treatment with EGCG activates the production of the nuclear factor of transcription Nrf2, which is responsible for protection against oxidative stress and inflammation of the endothelium [121].

The hepatocyte growth factor HGF and the receptor for this protein, which is known as c-Met, are involved in the regulatory pathway responsible for the invasion and metastasis of most human cancer cells. In tumor cells, c-Met accumulates in lipid rafts only after its phosphorylation. It has been demonstrated that EGCG can downregulate carcinogenesis by preventing the phosphorylation of the c-Met receptor. This activity was demonstrated only for catechins containing galloid moieties [122]. It was previously reported that luteolin can also block the phosphorylation of the c-Met receptor of tyrosine kinase, even though this flavonoid contains no galloid groups [123].

The well-known hypocholesterolemic effect of green tea can be due to the presence of gallocatechins [124,125]. It is known that cholesterol is normally removed from blood, delivered to the duodenum, and excreted from the body after its oxidation into bile salts catalyzed by cytochrome P450. However, considerable amounts of bile salts can be reabsorbed in the ileum with the apical sodium bile acid transporter ASBT. It was demonstrated that EGCG inhibits the ASBT transporter and thus decreases the presence of this protein in lipid rafts, where

the transport process takes place, which results in the normalization of the cholesterol content in the blood [126].

Quercetin can also influence the regulatory processes in caveolae. The anti-inflammatory activity of quercetin is explained not only by its antioxidative properties but also by its inhibition of nitric oxide production and its downregulation of various kinases present in rafts, including c-Jun, p38, Akt, Src, JAK-1, Tyk2, and NF-κB. Moreover, quercetin inhibits serine–threonine and tyrosine phosphatases [127] and ensures that toxic polychlorodiphenols (PCD) do not activate the caveolin-regulated signaling cascades responsible for inflammation and atherosclerosis. As was demonstrated in colon cancer cells, quercetin can induce the accumulation of the death receptors DR4 and DR5, which promote the TRIAL-induced apoptosis of tumor cells, in rafts [128]. Quercetin inhibits the expression of caveolin, CYP1A1, and the cell-adhesion molecules (VCAM-1) selectins E and C. Thus the protective effect of quercetin is explained by its direct influence on the caveolae [129]. Other flavonoids, such as the phytoestrogen genistein, can restore the raft levels of caveoline-1 and angiotensin receptor AT-1, which are decreased after ovariectomy in experimental hypertensive animals, which results in the normalization of the cardiovascular system [130].

8. Metal-chelating properties of flavonoids

8.1. Biological and medical relation

The antioxidative properties of flavonoids are based not only on their free-radical scavenging ability but also on their chelation of transient metals [131–133]. Moreover, flavonoid complexes with iron, cupper, and other cations reveal superoxide dismutase activity [134,135]. The protective properties of flavonoid–metal complexes have been demonstrated both in vitro and in vivo. For example, rutin complexes with Fe^{2+}, Fe^{3+}, Cu^{2+}, and Zn^{2+} to effectively protect the animal lung against asbestos-induced injury [136]. Complexes of morin with Pd(II) or Pt(II) are also active toward superoxide radicals [137].

Some metal complexes of flavonoids reveal toxicity to cancer or bacterial cells. For example, quercetin complexes with trivalent cations of rare-earth metals (La, Nb, Gd, Tb, Dy, Tm, and Y) were found to be toxic to tumor cells, likely due to their ability to specifically interact with DNA [138–140]. High antioxidant activity and ability to interact with DNA were also found for rare-earth Y(III) and Eu(III) complexes with naringenin-2-hydroxy benzoyl hydrazone ligand [141] or complexes of Ln(III) with hesperetin-4-one-(benzoyl) hydrazone. Complexes of morin with La(III), Gd(III), and Lu(III) revealed very high antibacterial activity, comparable to that of penicillin, against *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* [142]. The high protective ability of flavonoid–metal complexes revealed in experiments with cells, tissues, and animals [131–133,143,144] suggests perspectives regarding their medical use [145].

8.2. Physical and chemical properties of flavonoid–metal complexes

It is generally accepted that the two neighboring hydroxyls or neighboring carboxyl and hydroxyl groups of flavonoids are responsible for the metal chelating ability of these compounds. In ring B, the 3′ and 4′-hydroxyl groups, which are known as catechol groups, are very active in the chelation of metals. These catechol groups are present not only in catechins but also in quercetin, taxifolin, and some other flavonoids. In ring C, the 3-hydroxyl-4-carbonyl and 5-hydroxyl-4-carbonyl groups can also participate in metal chelation. The chelation forces are increased in an alkaline environment (pH 10) due to the deprotonation of hydroxyls. The above-described chelation sites were studied on many flavonoid–metal complexes, such as the complex of quercetin with Cu(II) [146]. Not all flavonoids have catechol groups, and the number of hydroxyls in flavonoid molecules can differ. For example, naringenin glycoside has only one position in the 5-hydroxyl-4-carbonyl group for metal chelation. In addition, it was found that the interaction of naringenin glycoside with Cu(II) increases its antioxidative and anti-inflammatory activities. Moreover, its complexation with cupper endows this compound toxic activity against tumor cells [147].

If a flavonoid has more than one site for metal chelation, the position of the metal atom and the stoichiometry of the complex are rather difficult to establish, and this point requires further investigation. Thus, complexes of Fe(II) and Fe(III) cations with quercetin may exhibit different stoichiometries and different sites for metal chelation. Molecular modeling [148] has revealed that the preferred site of chelation is located on the 3-hydroxyl-4-carbonyl group, followed by the 4-carbonyl-5-hydroxyl and the 3′- and 4′-carboxyl groups. Accordingly, iron can produce complexes with one, two, or three molecules of quercetin (Fig. 5).

The complexation of flavonoids with metal cations can considerably change their lipophilicity and interaction with the lipid bilayer. The distribution coefficient calculated for different complexes in octanol-water (CLogP) revealed that a complex of quercetin:iron with a stoichiometry of 1:1 is less lipophilic than free quercetin, although the lipophilicity obtained with different stoichiometries increased in the following order: 2:1 < 3:2 < 3:1 (see Table 1). The experimental analysis also revealed an increase in quercetin and taxifolin lipophilicity after chelation with iron(II), although the experimentally obtained values of LogP were considerably lower than those calculated using molecular models [19].

8.3. Interaction of flavonoid–iron complexes with lipid bilayer and proteins

Iron is an essential element of nutrition, and its deficiency causes the spread of anemia both in developing and in industrial countries. Polyphenols are among the factors that are potentially able to restrict the bioavailability of iron due to the production of low-soluble complexes [149]. For example, tea catechins prevent normal iron adsorption from the gut in populations that are already at risk of anemia but are not harmful to healthy people [150]. The iron-chelating abilities of different flavonoids are efficient for protection against oxidative stress in sickle cell anemia [151,152], rheumatoid arthritis [153], thalassemia, and Fanconi's anemia [154,155], which are disorders characterized by elevated concentrations of free iron cations in the blood.

Although the solubility of flavonoids in water is low, these compounds can interact with biological membranes, penetrate into the phospholipid bilayer, and influence the phase behavior of lipids. These molecules change the melting temperature of phosphatidylcholine and the bilayer/hexagonal H_{II} phase transition of phosphatidylethanolamine [156,157]. Metal cations can increase the lipophilicity of flavonoids and modify their influence on lipid-phase transitions. For example, complexes of quercetin with iron(II) increase the temperature of the bilayer/hexagonal H_{II} phase transition in phosphatidylethanolamine liposomes to a considerably stronger degree than free quercetin [19].

The observed changes in the temperature of the bilayer/hexagonal H_{II} phase transition of phosphatidylethanolamine may have an important biological effect, although it should be noted that this lipid is not present in lipid rafts but is preferentially located in the internal leaflet of the plasma membrane apposed to rafts [158]. The observed changes in the bilayer/hexagonal H_{II} phase transition may influence cell signaling through G protein-coupled receptors, including the adrenergic receptor [159] and rhodopsin [160]. The involvement of plant polyphenols in the regulation of G protein-coupled receptors through the lipid environment may help prevent Alzheimer's disease [161], numerous age-relative disorders [162], blood pressure disorders [163], and cancer [164]. The bilayer/hexagonal H_{II} phase transition may also control numerous processes related to membrane fusion [165] and the penetration of virus particles and peptide toxins via the membrane [166,167]. Moreover, the abovementioned transition can influence the antibacterial [168–170] and antiparasitic [171] activities of various compounds, including drugs.

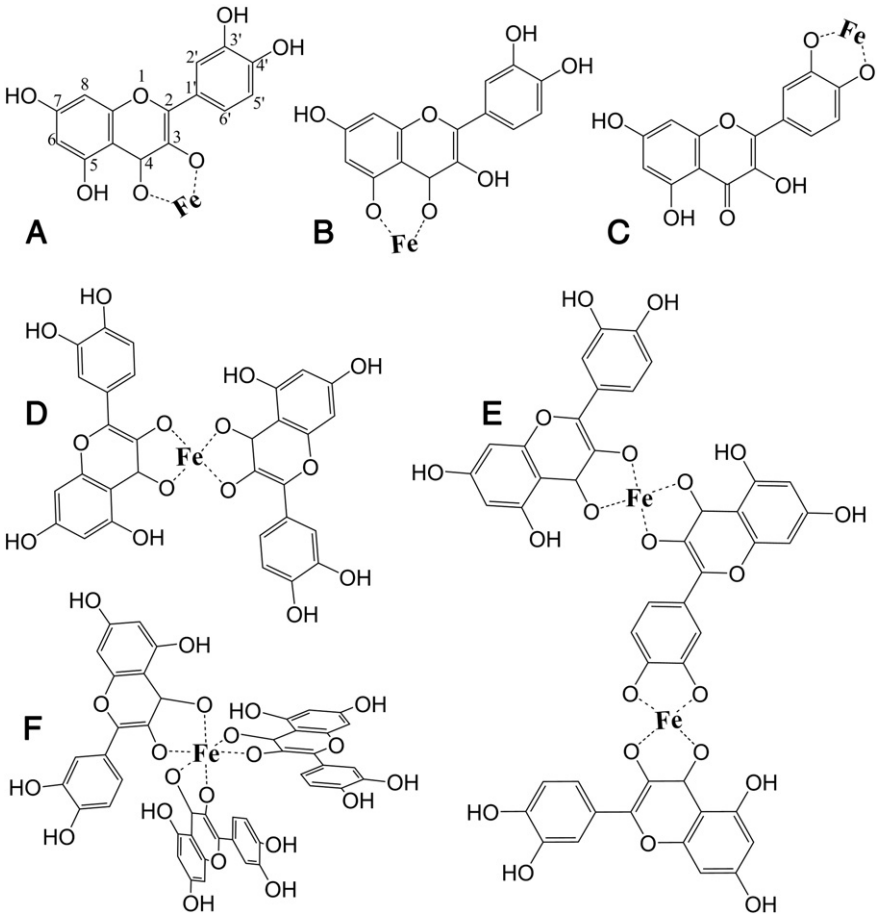

Fig. 5. Probable structure of some quercetin–Fe complexes with stoichiometries of 1:1 (a–c), 2:1 (d), 3:2 (e), and 3:1 (f) [148,198].

We should also mention the recently found ability of flavonoids to initiate liposome aggregation and fusion in the presence of iron(II) and calcium cations [20]. For example, freeze-fracture electron microscopy revealed the adhesion and fusion of small liposomes, which resulted in an increase in their size and the formation of gigantic liposomes (Fig. 6). When two or three flavonoid molecules interact with a metal cation, the lipophilicity of the complex increases because the most polar sites of flavonoid molecules are buried inside the molecular aggregate. This polar moiety containing an atom of a transient metal could produce a bridge exposed to water, whereas the hydrophobic parts of the flavonoids are attached to the adjacent bilayers. Thus, a flavonoid–metal complex functions as a molecular fastener that may connect two adjacent lipid bilayers. Cations of calcium may facilitate adhesion between membranes, but they interact with negatively charged phosphates located on the polar heads of lipids [20].

The ability of polyphenolic compounds, such as tannic acids, to initiate the aggregation and adhesion of membranes has been discovered [172,173]. It was demonstrated that tannin molecules can produce bridges between adjacent bilayers. Flavonoid molecules are considerably smaller than tannins, and a single flavonoid molecule cannot produce an interbilayer bridge, whereas two molecules connected by a metal atom can be involved in the processes of intermolecular

Table 1
Calculated distribution coefficients in octanol/water system (lipophilicity) obtained from molecular models of quercetin and complexes of quercetin with iron cations. Modeling in ChemBio3D Ultra software (Perkin Elmer, USA).

Compound	CLog P
Quercetin	1.30757
Quercetin/iron (1:1)	0.86626
Quercetin/iron (2:1)	3.47752
Quercetin/iron (3:2)	5.5498
Quercetin/iron (3:1)	6.08878

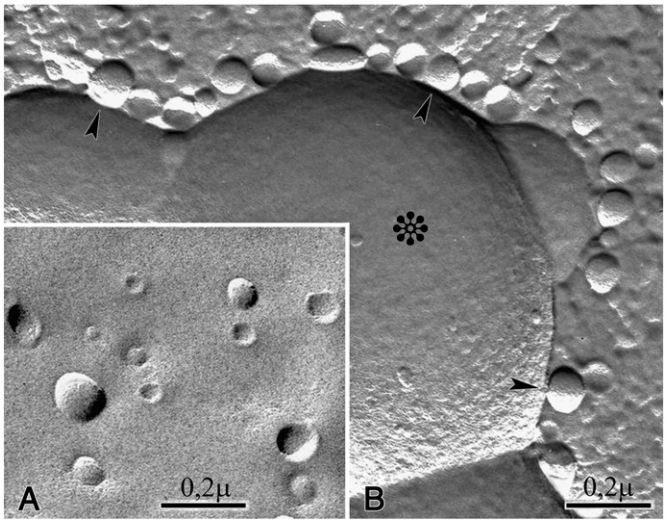

Fig. 6. Freeze-fracture electron microscopy of the adhesion and fusion of 100-nm phosphatidylcholine liposomes in the presence of quercetin–Fe^{2+} and Ca^{2+} [20]. (A) Original suspension of liposomes. (B) Liposomes after the addition of flavonoid and metals. The gigantic liposomes (marked by asterisk) appear as a result of membrane fusion. Some points of small liposome adhesion and fusion on the surface of a gigantic liposome are indicated by arrowheads.

interaction, as explained on the scheme shown in Fig. 7. We suggest that the hydrophobic sites (pockets) of proteins may also provide a possible hosting site for flavonoids, whereas metal atoms can be involved in intermolecular interactions, which may result in the clustering of proteins in membranes, protein adsorption on the membrane surface, or oligomerization of water-soluble proteins.

9. Involvement of flavonoids in intermolecular and intercellular coupling

Numerous studies have revealed the ability of flavonoids to participate in intermolecular and intercellular interactions, although our knowledge of the involvement of transient metal cations in the process is scarce. It was found that flavonoids can influence the polymerization of some proteins to produce protein fibers. For example, there is evidence of the ability of taxifolin to initiate the formation of stable collagen fibers from monomers of this protein [174]. Catechin gallates of green tea can effectively protect Vero cells against damage induced by *E. coli* enterotoxin by producing large insoluble aggregates of enterotoxin [175]. EGCG can induce the aggregation of erythrocytes through covalent catechol–protein adducts with the sulfhydryl groups of membrane proteins [176]. Some flavonoids, including hesperetin, naringenin, daidzein, and morin, increase the integrity of the tight junction barrier responsible for the functioning of intestinal epithelium Caco-2 cells through modulation of the protein–membrane association [177].

The antibacterial effect of flavonoids can be explained by the aggregation of bacterial cells and damage to the bacterial membrane. The aggregation of cells can decrease their access to oxygen and facilitate the accumulation of waste products to prevent proliferation and induce the initiation of cell death [178]. The aggregation of bacterial cells after their treatment with EGCG was accompanied by the anti-bactericidal activity of this flavonoid, whereas less-bactericidal flavonoids did not initiate aggregation processes [179]. As a result of protein aggregation, EGCG can inactivate toxic enzymes extracted from bacterial membranes [180]. Synthetic 3-arylideneflavanones were found to be highly active against *S. aureus*, *S. epidermidis*, and *E. faecalis* due to flavonoid-initiated bacterial cell aggregation and biofilm disturbance [181].

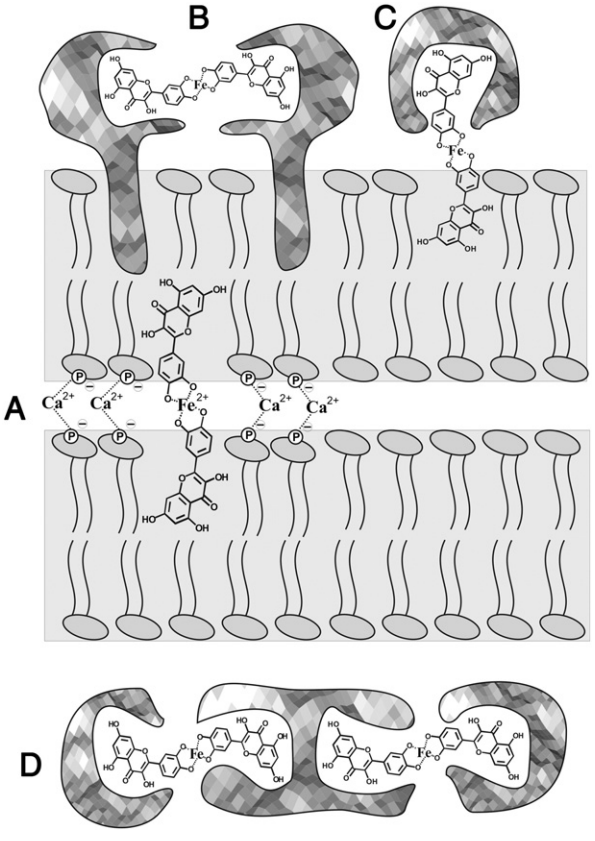

Fig. 7. A model of a quercetin–iron "fastener" that (A) holds together adjacent lipid bilayers. Calcium cations interact with the negatively charged phosphate groups of lipids and contribute to the interbilayer forces of adhesion, (B) initiates the aggregation of membrane proteins, (C) participates in the adsorption of proteins to the membrane surface, and (D) initiates the oligomerization or formation of water-soluble protein fibers. It is hypothesized that flavonoids penetrate into the hydrophobic site of the lipid bilayer or into hydrophobic protein pockets.

Despite the evidence presented above, there are numerous observations that flavonoids prevent the intermolecular interactions of proteins, the formation of cell membrane contacts, and membrane fusion. For example, it has been shown that the oligomerization of some proteins may cause mental disorders, including Parkinson's and Alzheimer's diseases. The protective effect of the flavonoids baicalein, apigenin, morin, and black tea extract is explained by their ability to prevent the oligomerization of human alphaS protein, which is responsible for Parkinson's disease [182]. Quercetin, green and black tea extracts, cyanidins, and extracts of grape seed are effective inhibitors of Abeta protein aggregation and the assembly of amyloid fibers, which are responsible for the development of Alzheimer's disease [183–186].

The flavonoids apigenin, quercetin, and cirsimaritin favor erythrocyte deformability and prevent their aggregation to ensure the maintenance of their filterability [187]. Soy isoflavones, naringin, quercetin, and many other flavonoids may inhibit platelet aggregation initiated by toxic compounds [188–190]. The flavonoid eupatilin, which is known as an anti-inflammatory compound, prevents the adhesion of monocytes and eosinophils to bronchial epithelial cells [191]. As was demonstrated on human hepatoma cells, the anticancer properties of baicalein can be explained by its ability to prevent the adhesion, migration, and invasion of cancer cells [192]. The inhibition of cell adhesion to fibronectin may explain the protective ability of EGCG against various retinopathies [193].

The prevention of membrane fusion is a mechanism through which flavonoids protect an organism against viral infection. For example, it has been demonstrated that theaflavins have the potential to be developed as effective topical drugs for the prevention of the HIV-1 viral fusion with the cell membrane mediated by the HIV-1 envelope protein [194]. EGCG from green tea significantly decreases the entry of the influenza A virus into nasal epithelial cells [195]. The flavonolignans silybin A and silybin B prevent liver infection with the hepatitis C virus by targeting multiple steps in the viral lifecycle, including by preventing the fusion of viral particles to membranes [196,197].

10. Conclusions

Flavonoids are polyphenolic compounds produced by plants for their protection against different environmental hazards. Animals and human do not produce flavonoids but consume them daily through food. Thus, throughout evolution, flavonoids are constantly present in our body. Although sometimes ignored, flavonoids can influence various cellular processes, including membrane transport, protein assembly, cell signal transduction, and gene expression. Flavonoids maintain our health and protect us against toxins and infections.

Flavonoids are able to penetrate into the hydrophobic and interphase sites of biological membranes, particularly compartments known as lipid rafts. The influence of flavonoids on the physical properties of the lipid bilayer may control the arrangement of membrane proteins and the formation of functional complexes responsible for cell signal transduction and the regulation of the metabolism.

Flavonoids are known as powerful antioxidants and chelators of transient metals involved in oxidation. Flavonoid complexes with iron cations are worthy of special consideration because both components are present in abundance in the human body. After complexing with metals, the antioxidative potential and lipophilicity of flavonoids may

increase, thereby facilitating the protection of membrane lipids against oxidation. Moreover, flavonoid–metal complexes may function as molecular "fasteners" that penetrate into the hydrophobic sites of membranes or proteins and initiate their adhesion and aggregation. These processes may participate in cell–cell interaction and protein clusterization and may provide protection against infection and disease. To obtain a better understanding of the involvement of flavonoids in the health control, their complexation with transient metals should be investigated in more detail.

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