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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).

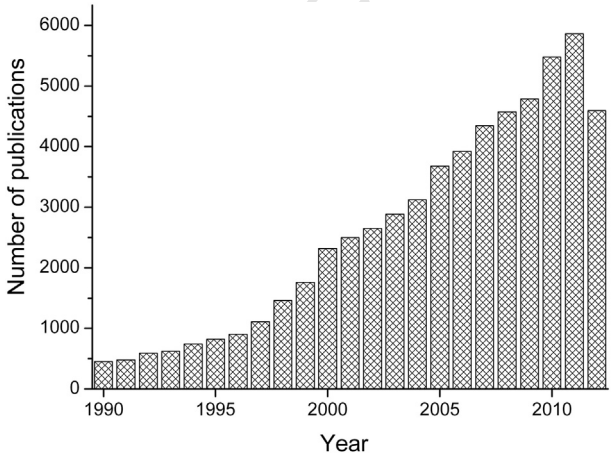

Fig. 1. Number of studies on flavonoids performed in different years according to PubMed (NCBI, MD, USA). The keyword "flavonoids" was used to search the database with the Reference Manager software (ICI ResearchSoft, USA).

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

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