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Review

Bioactive flavonoids in medicinal plants: Structure, activity and biological fate

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ABSTRACT

Flavonoids, a class of polyphenol secondary metabolites, are presented broadly in plants and diets. They are believed to have various bioactive effects including anti-viral, anti-inflammatory, cardioprotective, anti-diabetic, anti-cancer, anti-aging, etc. Their basic structures consist of C_6—C_3—C_6 rings with different substitution patterns to produce a series of subclass compounds, and correlations between chemical structures and bioactivities have been studied before. Given their poor bioavailability, however, information about associations between structure and biological fate is limited and urgently needed. This review therefore attempts to bring some order into relationships between structure, activity as well as pharmacokinetics of bioactive flavonoids.

1. Introduction

Flavonoids are a class of compounds presented broadly in nature. Concerns about their extensive profitable bioactive benefits, including anti-viral/bacterial, anti-inflammatory, cardioprotective, anti-diabetic, anti-cancer, anti-aging, have long been received great attention and well supported by numerous studies [1–4]. Till now, more than 9000 flavonoids have been reported [5], and their daily intake varies between 20 mg and 500 mg, mainly from dietary supplements including tea, red wine, apples, onions and tomatoes [6,7]. Flavonoids are frequently found as glycosylated or esterified forms, consisting of C_6—C_3—C_6 rings, namely rings A and B linked by three-carbon-ring C (Fig. 1) [8]. According to substitution pattern variations, flavonoids can thus be classified into different subclasses, providing an extremely diverse range of derivatives [8]. Although wide distribution and broad benefits, bioavailability of flavonoids is poor which may significantly influence the impact of nutritional effects, besides, information about pharmacokinetics in detail is limited. How to improve the issue is far from settled. This review attempts to bring some order into structure, activity as well as biological fate of flavonoids with particular emphasis on their relationships involved. Moreover, detailed information on structure-based drug design is crucial and required.

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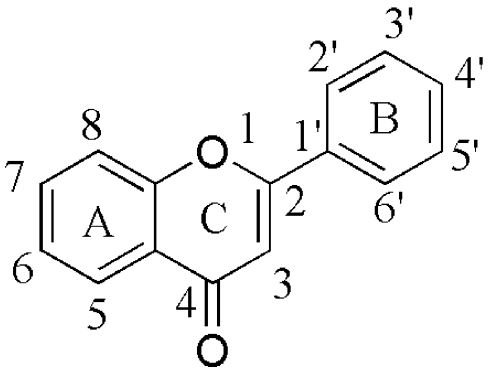

Fig. 1 – Basic skeleton or structure of flavonoids.

2. Chemical structure and classification of flavonoids

Flavonoids are a group of low molecular weight substances based on 2-phenyl-chromone nucleus (Fig. 2). They are biosynthesized from derivatives of acetic acids/phenylalanine by means of shikimic acid pathway. Traditionally, flavonoids are classified by oxidation degree, annularity of ring C, and connection position of ring B (Fig. 3). Flavones and flavonols contain the largest number of compounds, representing the narrow-sense flavonoids, namely 2-benzo-γ-pyrone category. Quercetin belongs to flavonol class, for example, has been studied most commonly. Flavanones and flavanonols possess saturated C_2═C_3 bonds, and often coexist with relevant flavones and flavonols in plants. Isoflavones, such as daidzein, are 3-phenyl-chromone substances. As key precursors of flavonoid biosynthesis, chalcones are ring C-opening isomers of dihydroflavones, responsible for color appearance of plants. Lacking typical structure of flavonoids, aurones are five-membered ring C benzofuran derivatives. Anthocyanidins are a group of important chromene pigments for characteristic color of plants, existing in the form of ions. Flavanols are reduction products of dihydroflavonols, especially with flavan-3-ols widely distribution in plant kingdom, also known as catechins. However, there are still other flavonoids without C_6—C_3—C_6 skeleton, for instance, biflavones, furan chromones and xanthones. Glycosides, with different category, number and connecting pattern, are predominate existing forms of flavonoids. Preferred glycosylation sites are associated with the structure of aglycones.

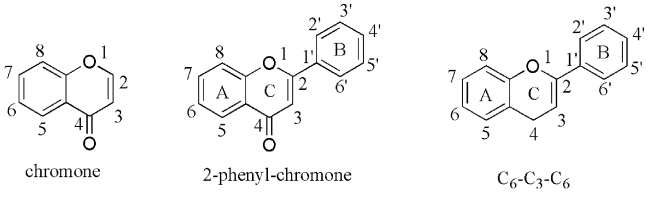

Fig. 2 – Chemical structures of the flavonoid classes.

3. Structure activity relationship (SAR)

A myriad of epidemiological studies have suggested a negative correlation between medicinal flavonoids consumption and development of various diseases [9–11], thereinto, flavonoids with typical structures can interact with enzyme systems involved in crucial pathways, showing effective polypharmacological behaviors [1,6,7]. Thus, it is not surprising that the relationships between chemical structures and activities have been extensively studied.

3.1. *SAR for anti-viral/bacterial activity*

Nowadays, bioactive flavonoids have been investigated for potent anti-viral/bacterial activity. For instance, therapeutic activities against influenza virus [6], canine distemper virus [12], hepatitis C virus [9], and *Escherichia coli* [13], have been attributed, largely, to chemical structures in particular patterns of methoxylation, glycosylation and hydroxylation [12,14]. Over years, related SAR researches have been characterized in diverse aspects. The C_2═C_3 double bond has been documented in most cases as a basic favorable element, which has been illustrated via the human fibroblast collagenase catalytic domain expression inhibitory activity loss of ampelopsin in comparison to quercetin [13].

In the case of hydroxylation, substitution style takes an important role. With regard to ring A hydroxylation, the positive role of 5-/7-hydroxyl derivatives has been suggested by six potential anti-H5N1 influenza A virus 5, 7-diOH flavonoid candidates [15], and less potent anti-human fibroblast collagenase catalytic domain (MMP1ca) effects of daidzein than quercetin [13]. Additionally, better MMP1ca inhibitory activity of 3′-OH ampelopsin/5′-OH gallocatechin gallate compared to daidzein/epicatechin gallate implys the contribution of hydroxylation in ring B [13]. Amongst others, a catechol group is the most common functional moiety. For example, better inhibitory activity of quercetin than morin in canine distemper virus inhibition [12], has provided a prominent therapeutic thought for novel drug synthesis. In the aspect of ring C, significant contribution of 3-OH has been observed (quercetin vs. luteolin) [16]. Apart from the site, the number of hydroxyl groups is another influencing factor. More hydroxyl groups results in lower hydrophobicity, which is obstructive for flavonoids to partition into biological membranes. Interestingly, sometimes certain hydroxyl group-rich-flavonoids do possess higher activity. The impact of hydrophobicity and electronic delocalization on the strength of hydroxylation assignment should be considered together, however. Additive hydroxyl groups might confer reduced hydrophobicity but higher C_3 charges which is a direct indicator for pharmacological activity [16].

As for methoxylation, its influence on membrane fluidity increase is correlated a large extent to the pathopoiesia of some viruses/bacteria, decreasing activity is therefore obtained. On this occasion, two polymethoxy flavonoids (PMFs) have been observed to exhibit decreasing anti-*E.coli* activity compared with related aglycones [16]. The study of *Amorpha fruticose* L. flavanones corroborates the previous experiment that bacterial neuraminidase inhibition of compound 2 is 70-fold stronger than unmethylated compound 3 [14].