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Review article

Recent discoveries of anticancer flavonoids

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ABSTRACT

In this review we report the recent advances in anticancer activity of the family of natural occurring flavonoids, covering the time span of the last five years. The bibliographic data will be grouped, on the basis of biological information, in two great categories: reports in which the extract plants bioactivity is reported and the identification of each flavonoid is present or not, and reports in which the anticancer activity is attributable to purified and identified flavonoids from plants. Wherever possible, the targets and mechanisms of action as well as the structure-activity relationships of the molecules will be reported. Also, in the review it was thoroughly investigated the recent discovery on flavonoids containing the 2-phenyl-4H-chromen-4-one system even if some examples of unusual flavonoids, bearing a non-aromatic B-ring or other ring condensed to the base structure are reported.

Contents

1. Introduction

Flavonoids are secondary polyphenolic metabolites occurring commonly in many fungi and plants. To the family of flavonoids belong several classes of compounds including anthoxanthins, in turn subdivided into two subgroups: flavones and flavonols;

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flavanones; flavanonols; flavans, in turn subdivided into three subgroups: flavan-3-ols, flavan-4-ols and flavan-3,4-diols; antocyanidins and isoflavonoids (Fig. 1).

The chemical structure of flavonoids is a 15-carbon skeleton which consist of two phenyl rings named A and B linked via a heterocyclic 4H-pyrane ring named C (Fig. 2). Modification to this basic structure, through different level of oxidation and substituents to the ring C, is responsible for the different classes of flavonoids (Fig. 2).

Examples of known flavonoids (Fig. 3) are: Apigenin **1** and Quercetin **2** (antoxanthins: flavone and flavonol respectively); Naringenin **3** (flavanone); Taxifolin **4** (flavanonol); Catechin **5**, Apiforol **6** and Leucocyanidin **7** (flavans: flavan-3-ol, flavan-4-ol and flavan-3,4-diol respectively); Malvidin **8** (anthocianidin) and Genistenin **9** (isoflavon).

The biosynthesis of flavonoids starts from the phenylalanine, which in turn comes from shikimic acid pathway. As reported in Fig. 4, the precursor phenylalanine leads to *p*-coumaril-CoA which reacts with 3 molecules of malonyl-CoA, coming from the fatty acid biosynthesis, to give the 4,2′,4′,6′-Tetrahydroxychalcone (Naringenin chalcone) and 4,4′,6′-Trihydroxychalcone (Isoliquiritigenin) [1–4]. The 4,2′,4′,6′-tetrahydroxychalcone is the precursor to obtain the flavanones which represent the precursor for all the other flavonoids (Fig. 4). Isoflavonoids can be obtained by two different biosynthetic pathways: from 4,4′,6′-trihydroxychalcone or from flavanones (Fig. 4) [2].

This class of compounds is important because both they are essential components to the humans and animal diet (flavonoids cannot be synthesized by humans and animals) and possess a therapeutic potential. They are present in almost all type of plants (Table 1) occurring virtually in all plant parts [5,6].

The versatile health benefit of flavonoids is well known. Antioxidant activity [7,8], weight management [9,10], cardiovascular disease protection [11,12], allergy [13], vascular fragility [14,15], viral and bacterial infection [16,17], antinflammatory activity [18–20], age-related neurodegenerative diseases prevention [21,22], anti-platelet aggregation effects [23] and ion transport effects [24] are examples of such benefits. Flavonoids are also useful as chemopreventive/chemotherapeutic agents. It is well known how high intake of fresh fruits and vegetables, rich in vitamins A, C, E, β-carotene, flavonoids and other constituents, confers cancer protection against several common human cancer such as: lung, breast, prostate, and colon cancers [25,26].

In fact, Woo et al. [27] showed how the intake of dietary flavonoids has protective effects on smoking-related cancer risk. It is also reported by Menezes et al. [28]. that flavonoids could act as chemopreventive agents interfering with several cancer mechanisms such as inhibition of cell growth and proliferation by arresting the cell cycle, induction of apoptosis and differentiation, or a combination of these mechanisms.

Moreover, there are several examples that emphasize how flavonoids are bioactive compounds able to interfere with the progression of cancer. A review of Durga et al. [29 and ref. cited therein] reported how various research groups showed the *in vitro* anticancer effect of various flavonoids on different cell lines (Table 2).

The researches just given above are some examples which show the anticancer activities of natural flavonoids and highlight their potential for the development of new chemotherapeutic agents.

In the present review we want to provide an overview of the anticancer activity of flavonoids, covering the time span of the last five years.

Literature survey on anticancer flavonoids revealed that in some cases the studies have been carried out by assaying the whole extract in which flavonoids are one of the principal fractions. Two possibilities may arise: a) the flavonoids content is expressed as “total flavonoids content” without identification of flavonoids structures, b) the flavonoids content has been isolated, and each flavonoids structure identified but only the whole extract assayed. Furthermore, in other works the authors have been able to isolate and identify one or more single flavonoids for which, the anticancer

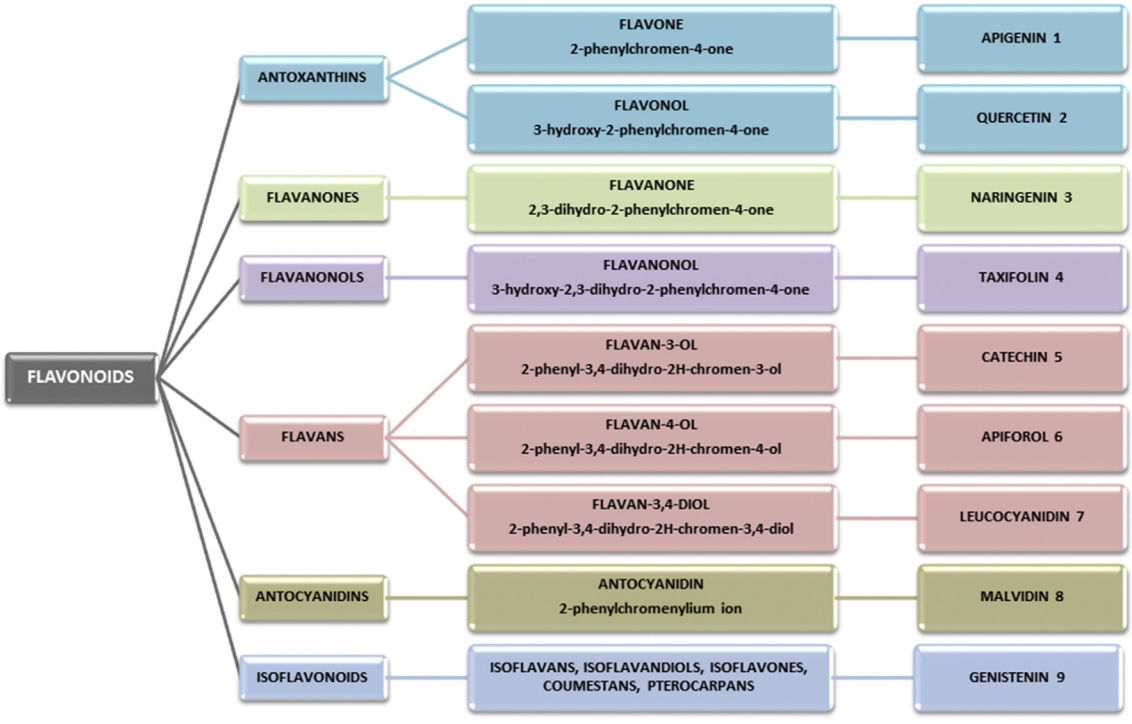

Fig. 1. Classification of flavonoids. The structures of compounds, take as examples of each class, are reported in Fig. 3.