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Invited review

Flavones: An important scaffold for medicinal chemistry

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ABSTRACT

Flavones have antioxidant, anti-proliferative, anti-tumor, anti-microbial, estrogenic, acetyl cholinesterase, anti-inflammatory activities and are also used in cancer, cardiovascular disease, neurodegenerative disorders, etc. Also, flavonoids are found to have an effect on several mammalian enzymes like protein kinases that regulate multiple cell signaling pathways and alterations in multiple cellular signaling pathways are frequently found in many diseases. Flavones have been an indispensable anchor for the development of new therapeutic agents.

The majority of metabolic diseases are speculated to originate from oxidative stress, and it is therefore significant that recent studies have shown the positive effect of flavones on diseases related to oxidative stress. Due to the wide range of biological activities of flavones, their structure–activity relationships have generated interest among medicinal chemists. The outstanding development of flavones derivatives in diverse diseases in very short span of time proves its magnitude for medicinal chemistry research. The present review gives detail about the structural requirement of flavone derivatives for various pharmacological activities. This information may provide an opportunity to scientists of medicinal chemistry discipline to design selective, optimize as well as poly-functional flavone derivatives for the treatment of multi-factorial diseases.

1. Introduction

Flavonoids are low molecular weight polyphenolic phytochemicals, derived from secondary metabolism of plants and play important role in various biological processes. They exhibit diverse type of properties that are beneficial for human health via interacting with a number of cellular targets involved in critical cell signaling pathways in the body. Research in the field of flavonoids has increased since the French paradox concept was formulated by French epidemiologists in the 1980s, i.e., lower cardiovascular mortality rate observed in Mediterranean populations in association with red wine consumption and a high saturated fat intake [1,2]. Flavonoids are components of a wide variety of edible plants, fruit, vegetables and of beverages such as tea, coffee, beer, and wine. So, *in-vitro* inhibition of LDL oxidation by flavonoids derived from red wine was demonstrated. Several other beneficial properties of flavonoids have since been ascertained as information about the mechanisms of flavonoids was scarce, but with time the flavonoids were explored hastily.

Flavonoids can be classified into various classes i.e. Flavonols (Quercetin, Kaempferol, Myricetin, Fisetin), Flavones (Luteolin, Apigenin), Flavanones (Hesperetin, Naringenin), Flavonoid Glycosides (Astragalin, Rutin), Flavonolignans (silibinin), Flavans (Catechin, Epicatechin), Isoflavones (Genistein, Daidzein), Anthocyanidins (Cyanidin, Delphinidin), Aurones (Leptosidin, Aureusidin), Leucoanthocyanidins (Teracacidin), Neoflavonoids (Coutareagenin, Dalbergin), Chalcones. All classes of flavonoids exhibits variety of biological activities, but among them, the flavones have been considerably explored. Various natural, semi-synthetic and synthetic derivatives of flavones have been synthesized and evaluated for several therapeutic activities like anti-inflammatory, anti-oestrogenic, antimicrobial [3], anti-allergic, antioxidant [4], anti-tumor and cytotoxic activities [5]. The majority of metabolic diseases are speculated to originate from oxidative stress, and it is therefore significant that recent studies have shown the positive effect of flavones on diseases related to oxidative stress, such as atherosclerosis, diabetes, cancer, Alzheimer's disease, etc. Some of the flavones of natural origin like Naringenin (Natural Female Support), Gingko Flavone glycosides (Gingko Smart), and synthetic origin like Flavopiridol are presently available in the market.

Flavones are present in fruits and vegetables which we consume inadvertently in our daily diet and they have a positive impact on our health without any major side effects. In order to explore

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diverse roles of flavones, investigating various methods for their synthesis and structural modification of flavone ring have now become important goals of several research groups. Thus, naturally obtained flavone moiety having a variety of biological activities can be taken as lead compound for the synthesis of semi- and purely synthetic flavone derivatives with different functional groups at different positions of flavone skelton.

2. Chemistry

Flavone is a class of flavonoids based on the backbone of 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one). The molecular formula of flavone molecule is $C_{15}H_{10}O_2$. It has a three-ring skeletons, C6–C3–C6, and the rings are referred to as A-, C-, and B-rings, respectively (Fig. 1). Flavones have three functional groups, including hydroxy, carbonyl, and conjugated double bond; consequently they give typical reactions of all three functional groups. Flavones are colorless-to-yellow crystalline substances, soluble in water and ethanol. They give yellow color solution when dissolve in alkali. Flavones are moderate-to-strong oxygen bases, and are soluble in acids due to the formation of oxonium salts having pKa values ranging from 0.8 to 2.45 [6]. Flavones have a planar structure with its C–O–C bond angle 120.9°. Its bond length between C–O is 1.376 Å and dihedral angle is around 179.2°.

Synonyms of flavone are 2-phenyl-4*H*-chromen-4-one; 2-phenyl-1-benzopyran -4-one. Flavones can react in several ways, including reduction reactions [7], degradation in the presence of base [8], oxidation [9], rearrangement [10], substitution [11,12], addition [13–15], condensation [16], reaction with organometallic reagents [17].

Several synthetic methods have been developed and modified to get products of high yield, purity and of the desired quality. Flavones can be synthesized by various synthetic schemes like Claisen–Schmidt condensation [18], Baker–Venkataraman-rearrangement [19,20], Ionic Liquid Promoted synthesis [21], Allan–Robinson [22], Vilsmeier–Haack reaction [23], Wittig reaction, Fries rearrangement and modified Schotten–Baumann reaction. Now a day, most of the flavones are synthesized based on the Baker–Venkataraman method. It involves the conversion of o-hydroxyacetophenone into phenolic ester, which undergoes an intramolecular Claisen condensation in the presence of a base to form β-diketone, which is cyclized to flavones by an acid-catalyzed cyclodehydration (Schemes 1 and 2).

Traditionally, flavones were synthesized with Baker–Venkataraman-rearrangement but these reactions undergo the use of strong bases, acids, long reaction time and low yields consequently Sashidhara et al. reported expedient, simplistic and alternate synthesis of medicinally important flavones in which 2-hydroxychalcones resulting from condensation between acetophenones and salicylaldehyde, undergo oxidative cyclization on heating in the presence of catalytic iodine and generating diversified flavones under solvent-free environmental friendly conditions [24] (Scheme 3).

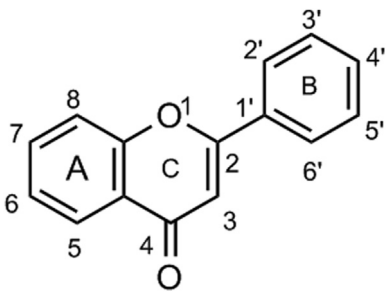

Fig. 1. Basic scaffold of flavone.

3. Biosynthetic pathway for flavones

Flavonoid biosynthesis starts with the condensation of 1 molecule of 4-coumaroyl-CoA and three molecules of malonyl-CoA yielding naringenin chalcone, carried out by the enzyme chalcone synthase (CHS). The two immediate precursors of the chalcone originate from two different pathways of primary metabolism. Coumaroyl-CoA is synthesized from the amino acid phenylalanine by three enzymatic steps, collectively called the general phenylpropanoid pathway, Malonyl-CoA is synthesized by carboxylation of acetyl-CoA, a central intermediate in the Krebs tricarboxylic acid cycle. The chalcone is consequently isomerized by the enzyme chalcone flavanone isomerase (CHI) to yield a flavanone. From this central intermediate the pathway diverges into several different classes of flavonoids [25] (Scheme 4).

4. Pharmacological activities of flavones

Flavones scaffold can be termed 'skeleton key' as it is an important core in many compounds acting at different targets to elicit varied pharmacological properties with various substitution patterns (Fig. 2). It is the diversity of this structure that gives flavones wide range of biological activity. Due to the wide range of biological activities of flavones, their structure–activity relationships have generated interest among medicinal chemists, and this has culminated in the discovery of several lead molecules in numerous disease conditions. This review gives a comprehensive account of SAR or structural requirement of flavone derivatives, necessary for wide biological activity spectrum.

4.1. Anti-oxidant

The high levels of free radicals in living systems are able to oxidize bio-molecules, leading to tissue damage, cell death or various diseases such as cancer, cardiovascular diseases, arteriosclerosis, neural disorders, skin irritations and inflammations [26]. Free radicals are highly reactive and therefore can attack membrane lipids, generating carbon radicals and produce peroxy radicals which cause lipid peroxidation. Therefore, a single radical may damage many molecules by initiating lipid peroxidation chain reactions. To oppose the vicious effect of free radicals, the body has a number of antioxidant defense mechanisms in the form of enzymes such as superoxide dismutase and catalase, copper and iron transport proteins, as well as water-soluble and lipid-soluble antioxidants [27]. It was studied that imbalance between free radicals and the antioxidant defense mechanism is associated with several human diseases.

Antioxidants may act with two mechanisms: prevention of initiation of oxidation, or as chain breaking antioxidants. Prevention of initiation of oxidation occurs by inhibiting superoxide anion production, degrading hydrogen peroxide and chelating or reducing metal ions, while chain breaking antioxidants act by scavenging radicals, mostly hydroxyl radicals, thereby inhibiting the chain of oxidative events that leads to damage of lipid membranes, proteins and DNA [28]. Oxidative species and free radical involve in the pathophysiology of numerous diseases like in neurodegenerated disorders, cardiovascular, cerebrovascular, autoimmune disorders like diabetes, rheumatoid arthritis, psoriasis etc. Therefore, various natural as well as synthetic antioxidants are used to scavenging free radicals.

It was reported that flavones have well known antioxidant activity; and can act by several pathways. Therefore, flavones are