Classification and Biosynthesis of Flavonoids

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Flavonoids are mainly found in plant cell vacuoles in the form of *C*-glycosides or *O*-glycosides. The basic molecular structure of flavonoids depends upon their basic C6–C3–C6 skeleton. Flavonoids are classified into seven subclasses based on modifications to their basic skeletons; these subclasses include flavones, flavanones, isoflavones, flavonols, chalcones, flavanols, and anthocyanins.

flavonoids biosynthesis pathway classification biological activity application

1. Flavonoid Classification

1.1. Flavones

Flavones, one of the largest classes of flavonoids, consist of 4H-chromen-4-one bearing a phenyl substituent at position 2. Flavones mostly occur as 7-*O*-glycosides, which are found in celery, parsley, red pepper, chamomile, mint, and ginkgo [1][2][3]. Apigenin and luteolin are two common flavones (**Figure A1**). In nature, apigenin is usually found in a glycosylated form, with a sugar moiety attached to the tricyclic core structure via hydroxyl groups (*O*-glycosides) or directly to carbon (*C*-glycosides) [4]. The principal ingredients of apigenin are glycosylated apiin, apigenin, vitexin, isovitexin, or rhoifolin. Apigenin can scavenge free radicals and regulate antioxidant enzyme activity in pancreatic cells, and apigenin can decrease inflammation in cancer, neuroinflammation, and cardiovascular diseases [5][6].

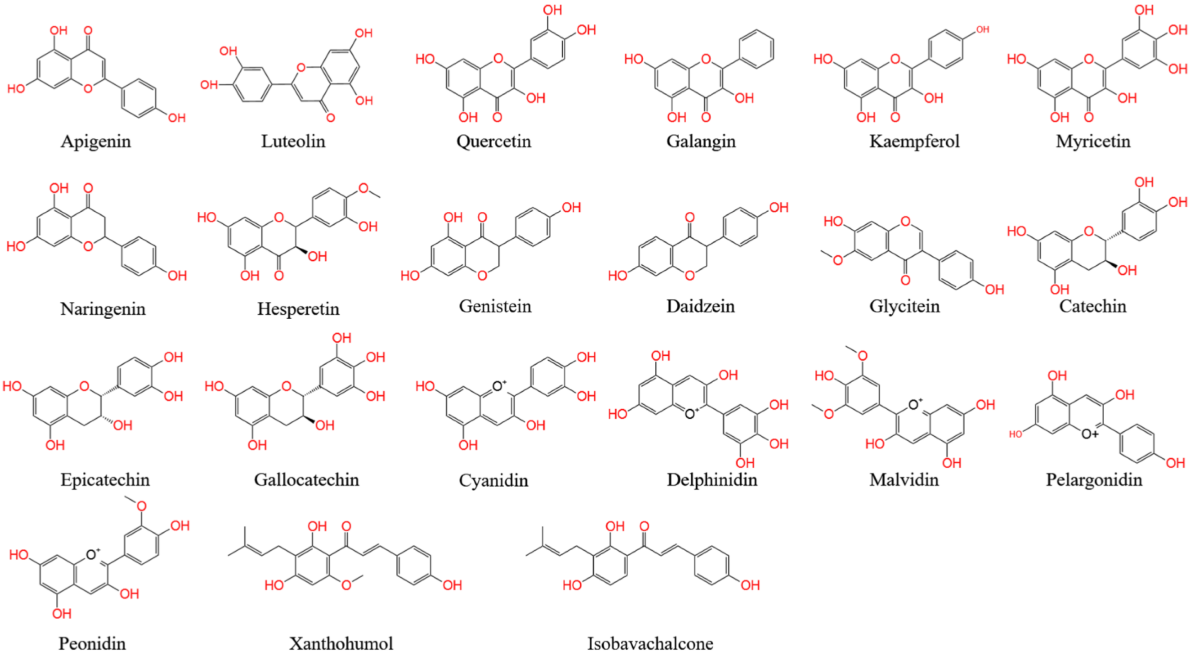

Figure A1. The Basic Structure of Flavonoids.

1.2. Flavonols

Flavonols, also called 3-hydroxy flavone, can be identified by specific substitutions in their A- and B-rings, which are connected by a three-carbon chain [7]. Flavonols possess hydroxyl groups at positions 5 and 7 in the A-ring and are mainly present in epidermal cells to protect DNA against UV-induced damage [8]. Four types of flavonol compounds (quercetin, galangin, kaempferol, and myricetin) are mainly distributed in vegetables and fruits, such as asparagus, onions, lettuce, broccoli, tomato, and apples (**Figure A1**) [9]. Flavonols exhibit interesting biological activities, including antioxidant, antibacterial, cardioprotective, anticancer, and antiviral activities. Dietary flavonols can significantly decrease the risk of gastric cancer in smokers and in women (**Figure A1**).

1.3. Flavanones

Flavanones (dihydro-flavones) possess a saturated C-ring [10]. The saturated double bond between positions 2 and 3 in the C-ring represents the only structural difference between flavanones and other flavonoid compounds [11]. Flavanones are mainly distributed in citrus fruits, including oranges, lemons, mandarins, grapefruits, clementines, and limes [12]. Flavanones contain hydroxyl groups at positions 5 and 7 in the A-ring and possess hydroxyl/methoxy substituents at the C3 or C4 positions of the B-ring [13]. The defining characteristic of flavanones is a disaccharidic moiety linked to the seven positions of aglycone [14]. Depending on their structural differences, flavanones can occur in the form of naringin, naringenin, hesperidin, hesperetin, pinocembrin, likvirtin, and eriodictyol [15]. Among them, naringenin and hesperetin, as the main dietary flavanones, occur almost exclusively in citrus fruits (**Figure A1**) [12][16]. Naringin can increase the activity of antioxidant enzymes (CAT, PON, GPx, and SOD) and enhance the immune system. Furthermore, naringenin and hesperetin have been shown to recover impaired thyroid function in rats.

1.4. Isoflavonoids

Isoflavones have a B-ring at the C3 position of the heterocyclic C-ring of the diphenylpropane (C6–C3–C6) backbone, which represents their only chemical structural difference from other flavonoids [17]. Isoflavonoids are characteristic metabolites of leguminous plants and play essential roles in nodule induction and microbial signaling in legumes [18][19]. Isoflavones are classified into three groups: genistein, daidzein, and glycitein (**Figure A1**) [20]. The molecular structure of isoflavones is similar to that of animal estrogens. Isoflavones are phytoestrogens that exhibit potent estrogenic activity. Phytoestrogens are similar in structure to the human female hormone 17-β-estradiol in that they bind to estrogen receptors [21]. In addition, isoflavones possess a strong antioxidant activity, which can decrease the risk of cancers by inhibiting free radical-induced DNA damage [21].

1.5. Flavanols

Flavanols, also called catechins or flavan-3-ols, are characterized by a hydroxyl group at position 3 in the C-ring [22]. Flavanols lack a double bond between positions 2 and 3 in the C-ring [23]. Several flavanols, including catechin, gallocatechin 3-gallate, gallocatechin, epicatechin, epicatechin 3-gallate, catechin 3-gallate, and epicatechin 3-gallate, are widely distributed in many fruits (e.g., apples, bananas, pears, and blueberries) [24][25]. Flavanols can protect blood vessels against tobacco by increasing the content of NO in blood vessels. A flavanol-rich diet can facilitate the permanent improvement of endothelial function and prevent the development of cardiovascular diseases [26][27].

1.6. Anthocyanins

Anthocyanins, as glycosylated polyphenolic compounds, are a group of soluble vacuolar pigments that possess a range of colors, from orange, red, and purple to blue, depending on the pH of the micro-environment of the flowers, seeds, fruits, and vegetative tissues [28]. The position and number of hydroxyl and methoxyl groups present as substituents in the flavylium structure result in different anthocyanins (**Figure A1**). Thus, over 650 anthocyanins have been identified in many plants [29]; these are grouped into five items, including cyanidin, delphinidin, malvidin, pelargonidin, and peonidin, and their corresponding derivatives [30]. Anthocyanins are mainly found in the outer cell layer of various fruits and vegetables, such as blackcurrants, grapes, and berries [31][32]. The antioxidant ability of anthocyanins is associated with their ring orientation and the position and number of free hydroxyls around the pyrone ring. Anthocyanins play important roles in visual acuity, cholesterol decomposition, and the reduced risk of cardiovascular disease in humans [33][34]. In addition, anthocyanins are commonly used as food colorants.

1.7. Chalcones

Chalcones (1,3-diaryl-2-propen-1-ones) are natural open-chain flavonoids, carrying up to three modified or unmodified C5-, C10-, and C15-prenyl moieties on both their A and B-rings. These bioactive products are widely distributed in the Fabaceae, Moraceae, Zingiberaceae, and Cannabaceae families [5]. They exhibit a wide spectrum of pharmacological effects, including antioxidant, antibacterial, anthelmintic, antiulcer, antiviral, antiprotozoal, and anticancer effects [35]. Chalcones are precursors of flavonoids and isoflavonoids. Their structural features are easily constructed from simple aromatic compounds. Their prominent bioactivity has inspired the synthesis of chalcone analogs, as well as minor structural modifications to natural chalcones; these compounds form a large collection of bioactive chalcone derivatives [36]. Xanthohumol and isbavirachalone are two representative derivatives that exhibit abundant biological and pharmacological activity (**Figure A1**) [33].

Generally, the number and position of –OH groups have a great influence on flavonoid bioactivity. The –OH groups can link to the carbon atoms of the benzene ring (3,5,7, and 3′,4′-dihydroxy substitution pattern), which directly determines the bioactivity of flavonoids. Moreover, the position of the –OH group also influenced the flavonoid bioactivity. The most effective radical scavengers are flavonoids with the 3′,4′-dihydroxy substitution pattern on the B-ring and/or hydroxyl group at the C-3 position. In addition, the C2–C3 double bond is not necessary for high activity. Flavanols lacking the C2–C3 double bond displayed strong activity. The presence of a 3 –OH group significantly enhances the bioactivity.

2. Flavonoid Biosynthesis in Plants

2.1. Flavonoid Biosynthetic Pathways

Flavonoid synthesis occurs at the junction of the shikimate pathway and the acetate pathway. The former can generate *p*-coumaroyl-CoA, and the latter regulates C_2-chain elongation [37] (**Figure 1**). Phenylalanine ammonia-lyase (PAL) deaminates phenylalanine to ammonia and cinnamic acid [38]. Then, C4H (cinnamic acid 4-hydroxylase) catalyzes the production of 4-coumaric acid [39], and 4CL (4-coumaric acid: CoA ligase) converts 4-coumaric acid to form 4-coumaroyl-CoA, which is a key enzyme in the phenylpropanoid metabolic pathway that regulates the biosynthesis of lignin and flavonoids [40].

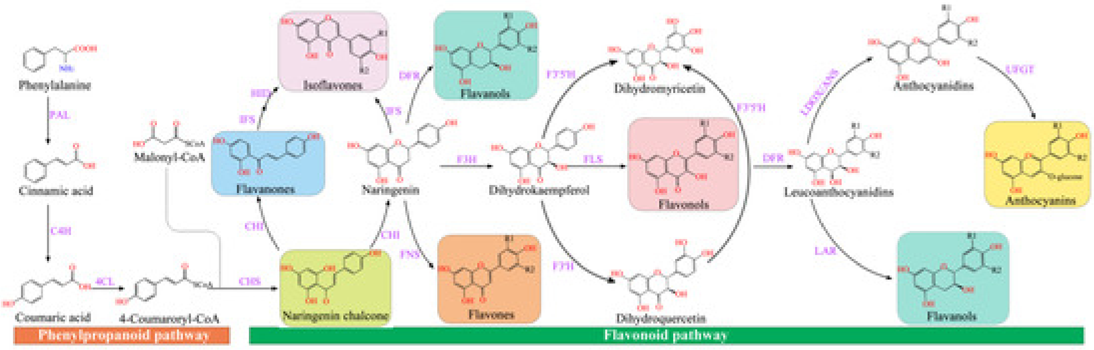

Figure 1. Flavonoid synthesis pathway. CHS (chalcone synthase) can catalyze three molecules of malonyl-CoA and one molecule of *p*-coumaroyl-CoA to form naringeninchalcone [41]. Malonyl-CoA is an important precursor for the synthesis of natural products, including flavonoids and polyketides [42]. CHI (chalcone isomerase) converted naringenin-chalcone into flavanones [43]. Naringenin, as an important flavonoid skeleton, is catalyzed by FNSI and FNS II (flavone synthase I and flavone synthase II) and IFS (isoflavone synthase) to form flavones and isoflavones, respectively [44]. Furthermore, flavanone-3-hydroxylase (F3H), flavonol 3′-hydroxylase (F3′H), and flavonol 3′5′-hydroxylase (F3′5′H) catalyzed naringenin to generate dihydro-myricetin, dihydro-kaempferol, and dihydro-quercetin, respectively [45]. The FLS (flavonol synthase) converted dihydroflavonols into flavonols (kaempferol,

quercetin, and myricetin), which was catalyzed by the dihydroflavonol 4-reductase (DFR) to generate leucoanthocyanidins [46], which was catalyzed by leucoanthocyanidin dioxygenase (LDOX) to produce anthocyanidins [47]. Anthocyanidins and leucoanthocyanidins were further converted to proanthocyanidins catalyzed by leucoanthocyanidin reductase (LAR) and anthocyanidin reductase (ANR), respectively [48]. Modification of anthocyanins is responsible for the stabilization of vacuolar anthocyanins, including glycosylation, methylation, and acylation [49].

2.2. Transcriptional Regulation of Flavonoid Synthesis

Flavonoid biosynthesis is tightly regulated by biosynthetic enzymes and regulatory transcription factors (TFs) [50]. Several TF families have been reported to be involved in regulating flavonoid biosynthesis in plants, including WRKY, Dof, MADS-box, bZIP, MYB, bHLH, WD40, and NAC (**Table 1**) [51]. Plant MYBs are characterized by a highly conserved MYB DNA-binding domain and are further classified into four groups based on the position and number of MYB repeats: 1R-MYB, 2R-MYB, 3R-MYB, and 4R-MYB [52]. Among them, R2R3-MYB TFs are involved in regulating the expression of structural genes in the flavonoid pathway [53]. For example, transgenic tobacco overexpressing *NtMYB3* from *Narcissus tazetta* can reduce the content of flavonoids by inhibiting the expression of *FLSs* [54]. Transgenic *Arabidopsis* overexpressing *GbMYB2* from *Ginkgo biloba* can decrease flavonoid accumulation by inhibiting the expression of some structural genes (e.g., *GbPAL*, *GbFLS*, *GbANS*, and *GbCHI*) [55]. Yan et al. revealed that soybean *GmMYB100* negatively regulated flavonoid biosynthesis by inhibiting the activities of CHS and CHI promoters [56]. In addition, the overexpression of *PpMYB17* in pear calli was found to bind and activate the promoters of structural genes of *PpCHS*, *PpCHI*, *PpF3H*, *PpFLS*, and *PpUFGT* under light conditions, which enhanced the biosynthesis of flavonoids [57]. Transgenic tobacco overexpressing *FtMYB31* from *Fagopyrum tataricum* increased the expression of *CHS*, *F3H*, and *FLS* genes and promoted the accumulation of flavonoids [58]. The overexpression of *SbMYB8* from *Scutellaria baicalensis* in transgenic tobacco promoted the expression of the *SbCHS* gene, increased flavonoid content, and enhanced the activities of antioxidant enzymes in transgenic tobacco [48]. Furthermore, bHLH TFs play essential roles in regulating the biosynthesis of flavonoids. *CsMYC2* was able to promote flavonoid biosynthesis by increasing the expression of the *UFGT* gene [59]. *MdbHLH3* promoted anthocyanin accumulation and fruit coloration in response to low temperatures in apples [60]. In addition, MBW complexes (MYB-bHLH-WD40) regulate flavonoid biosynthesis in different plants [49][61]. The TT2–TT8–TTG1 complex plays a major role in developing seeds and also plays an important role in regulating the expression of LBGs (*DFR*, *LDOX*, *TT19*, *TT12*, *AHA10*, and *BAN*) [62]. Moreover, the MBW complex exhibits tissue-specific regulation of the expression of the genes involved in flavonoid biosynthesis [63]. The MYB5–TT8–TTG1 complex is active in the endothelium, regulating *DFR*, *LDOX*, and *TT12* expression, whereas the TT2–EGL3/GL3–TTG1 complexes regulate the expression of *LDOX*, *BAN*, *AHA10*, and *DFR* in the chalaza [63].

Table 1. Pharmacological activities of flavonoids.

Flavonoids	Classification	Pharmacological Activity	Sources of Plant	References
Proanthocyanidins	anthocyanins	antioxidant, anti-inflammatory, antibacterial,	grapes, apples, sorghum, cherries, and other	[64]

Flavonoids	Classification	Pharmacological Activity	Sources of Plant	References
		antifungal and anti-cardiovascular	natural plant	
Cyanidin	anthocyanins	anti-inflammatory, antiviral, and anticancer	black rice, black beans, purple potatoes, blueberries	[65]
Curcumin	curcuminoids	anti-inflammatory and anticancer	Curcuma longa	[66]
Methyl chalcone	chalcones	anti-inflammatory and anticancer	apple, citrus, soybean, ginger, mulberry	[67]
Trans-chalcone	chalcones	anti-inflammatory and anticancer	apple, citrus, soybean, ginger, mulberry	[67]
Xanthohumol	chalcones	anti-cardiovascular and antiviral	Humulus lupulus	[68]
Licochalcone	chalcones	antibacterial and antifungal	Glycyrrhiza uralensis	[69]
Catechin	flavanols	antioxidant, anti-inflammatory, antiviral, and anti-cardiovascular	Camellia sinensis	[70][71][72]
Epigallocatechin gallate	flavanols	antioxidant, antibacterial, antifungal, anti-cardiovascular, and antiviral	Camellia sinensis	[73][74][75]
Naringin	flavanones	antioxidant, anti-inflammatory, anti-cardiovascular, and antiviral	lemons, oranges, grapefruits, citrus	[67][73][76][77][78][79]
Hesperidin	flavanones	anti-inflammatory, anti-cardiovascular, and antiviral	lemons, limes, oranges, grapefruits, citrus	[76][77][80][81]
Diosmin	flavanones	anti-inflammatory	citrus fruits	[82]
Orientin	flavanones	anti-inflammatory	Trollius chinensis, Cajanus cajan, Crataegus laevigata	[83]
Vitexin	flavanones	antioxidant, anti-inflammatory, and anticancer	Ficus deltoid, Spirodela polyrhiza	[83]

Flavonoids	Classification	Pharmacological Activity	Sources of Plant	References
Acacetin	flavanones	anti-cardiovascular, anticancer, and antiviral	Acacia farnesiana	[84][85]
Silymarin	flavanones	antioxidant, anti-cardiovascular, and antiviral	Silybum marianum	[86][87]
Liquiritigenin	flavanones	anti-inflammatory, antiviral, and anticancer	Glycyrrhiza uralensis	[88]
Isorhamnetin	flavanones	antiviral and anticancer	Ginkgo biloba, Hippophae rhamnoides	[85]
Apigenin	flavones	antibacterial, antifungal, and antiviral	Apium graveolens	[89][90][91][92]
Morin	flavones	antioxidant and anti-inflammatory	Cudrania cochinchinensis, Maclura pomifera	[93]
Baicalin	flavones	Anti-cardiovascular, antibacterial, and antifungal	Scutellaria baicalensis	[74][94]
Luteolin	flavones	anti-inflammatory, anti-cardiovascular, and antiviral	Dracocephalum integrifolium, Lonicera japonica, Capsicum annuum	[92][95]
Fisetin	flavonols	antioxidant	strawberry, apple, onion, cucumber, and other fruits and vegetables	[96]
Quercetin	flavonols	antioxidant, anti-inflammatory, anti-cardiovascular, antibacterial, and antifungal	vegetables, fruit, seeds, nuts, tea, and red wine	[71][80][97][98] [99][100][101]
Rutin	flavonols	antioxidant, anti-inflammatory, and antiviral	rue, tobacco, jujube, apricot, orange, tomato, buckwheat, and citrus fruits	[70][80][86][87]
Kaempferol	flavonols	antioxidant, anti-inflammatory, antibacterial, antiviral, and anticancer	fruits, vegetables, herbs, and other natural plants	[70][93][102] [111]
Myricetin	flavonols	antioxidant, anti-inflammatory, and anti-	Myrica rubra	[93][103][104]

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structural genes of *DFR*, *LDOX*, *TT19*, and *PAP1* to increase the content of flavonoids in plants [113]. Apple callus overexpressing *MdWRKY11* was able to increase the expression of *F3H*, *FLS*, *DFR*, *ANS*, and *UFGT* and promote the biosynthesis of flavonoids and anthocyanins [114].

Flavonoids	Classification	Pharmacological Activity	Sources of Plant	References
		cardiovascular		
Glabrol	isoflavane	antibacterial and antifungal	Glycyrrhiza uralensis	[69]
Genistein	isoflavone	antioxidant, antifungal, antiviral, and anticancer	soybeans and other plants	[80][105][106]

regulating indirectly [115] [115] found to [116]. miRNAs directly cleave structural genes (SG) for flavonoid synthesis, thereby negatively regulating the accumulation of flavonoids, including miR396-targeting UFGT, miR172-targeting 4CL, and miR829.1-targeting CHS [117]. The miRNA-directed cleavage of TFs involved in flavonoid synthesis through miRNA–TF–SG regulatory networks such as miR156–SPL–F3H, miR828/TAS4–MYBs–DFR, and miR858–MYBs–CHS/FLS [117][118].

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