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Flavones: Flavonoids Having Chemico-Biological Properties with a Preview into Anticancer Action Mechanism

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Abstract

Flavones belong to the flavonoids class of plant polyphenols. Owing to their widespread distribution in plants, such as fruits, vegetables, herbs, spices, and beverages (tea, coffee, and wine), these compounds are consumed by human beings in large amounts through daily nutrition. This group of compounds occupies an inimitable position in the realm of natural, semisynthetic, and synthetic organic chemistry as well as biological sciences owing to their diversified valuable role in human health and their distinctive role in plants. Their structural features are responsible for the biochemical effects and therapeutic applications attributable to immune modulation and prevention of many diseases in humans. In this chapter, we address the requisite structural features of flavones for their biological and pharmacological significance in terms of structure activity relationship and chemical synthesis along with biosynthetic approaches and biological properties of some chemically modified derivatives. Also, the chapter highlights the mechanistic insight into the action of flavones mediating anticancer therapeutic effects.

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Flavones · Structure-function relationship · Chemical synthesis · Biological properties · Anticancer effects · Mechanism

4.1 Introduction

Flavonoids are natural products that belong to the secondary metabolites phytochemical class having a polyphenolic structure and are currently consumed in huge quantities in daily nutrition. Among the flavonoids, flavones and flavonols delineate the enormous subgroups, and the versatile health benefits related to them have been reported in various studies. They are also liable for protecting and maintaining various properties of foods as well as plants, such as vivid color, taste, fat oxidation, vitamins, and enzyme preservation. Among these subclasses of flavonoids, flavones also play a significant role in plants and humans and possess various pharmaceutical, therapeutic, and nutraceutical properties due to their various biological actions, such as inhibition of allergic or inflammatory mediators, protection from abiotic and biotic stress conditions, inhibition of the NFκB pathway, interaction with nucleic acids and proteins, reduction of ROS, reduction of microRNA155 (miR155) expression, and agonists of ERRs (estrogen-related receptors) (Zhang et al. 2013; Moreira et al. 2017; Arredondo et al. 2015; Sharma et al. 2018a).

4.2 Structural Features

Structurally, flavone has a 2-phenylchromane nucleus (C_6–C_3–C_6) skeleton and it consists of two benzene rings (ring A and B) interrelated by a closed pyran ring (C ring) of a three carbon chain that amalgamates with ring A. Besides these features, a C_2=C_3 double bond and 4-Oxo group in ring C with the other groupings of multiple hydroxyls, –*O*-acetyl, –*O*-sulfate, –*O*-methyl, and –*C* or –*O*-glycoside group substituents are present on the basic skeleton of flavone. This class of compounds consists of aglycones, which are the basic structures of these compounds (apigenin, luteolin, chrysin, etc.), and their substituted congeners, such as sulfonated, acetylated, and methylated along with glycosylated derivatives (Fig. 4.1, Table 4.1) (Moreira et al. 2017; Arredondo et al. 2015; Singh et al. 2014; Teles et al. 2018; Correia-da-Silva et al. 2013). Apigenin, Luteolin, chrysin, and their different substituted congeners are abundantly extant in common fruits, vegetables, spices, and herbs, including parsley, onions, iceberg, celery, peppermint, thyme, celeriac, oranges, lettuce, tea, chamomile, wheat sprouts, etc. The most abundant flavones in the diet exhibit prolific biochemical effects against Cdk5 complexes, amyloid, protein kinase C, protein tyrosine kinases, adenylate cyclase, cyclooxygenases along with pharmacological effects, namely antioxidative, anticancer, anti-inflammatory, antitumor, antiviral, antibacterial, etc. (Funakoshi-Tago et al. 2011; Dundar 2015; Singh et al. 2014; Arredondo et al. 2015; Verma et al. 2012; Moreira et al. 2017;

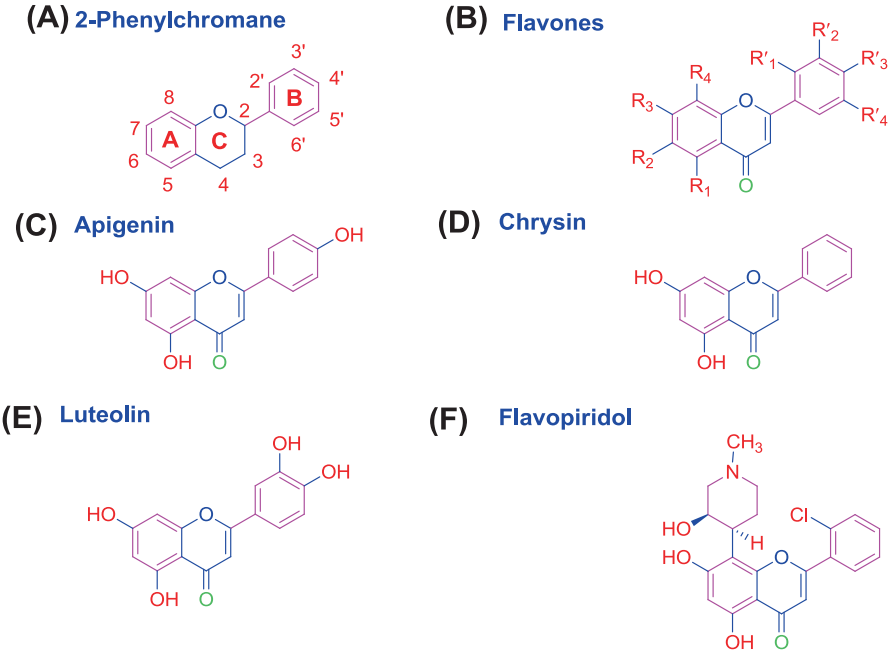

Fig. 4.1 Flavones consisting of the basic carbon skeleton (**a**) as well as substitution pattern in flavones subclass (**b**) with chemical structure of apigenin (**c**), chrysin (**d**), luteolin (**e**), and flavopiridol (**d**).

Zapata-Torres et al. 2004; Malisauskas et al. 2015; Zhang et al. 2013; Bhagwat et al. 2013; Southon et al. 1994; Teles et al. 2018; Correia-da-Silva et al. 2013). Natural flavones constitute an enormous segment of natural products and have a broad range of significant biological properties with low toxicity. The significance of flavones has led to the development of new compounds as magic bullets that possess significant biological and pharmacological properties. Flavoperidol (alvocidib) is a total synthetic flavone and is considered as a member of this family on the basis of a natural product (rohitukine) structure isolated from *Dysoxylumbinectariferum* Hook. f. (Meliaceae). It inhibits cyclin-dependent kinases CDK1, CDK2, and CDK4 and exhibits a potent inhibitory effect toward CDK9 (Cragg and Newman 2008; Zeidner et al. 2015; Zeidner and Karp 2015; Wiernik 2016). Several preclinical and clinical trials have been conducted for evaluating the significant benefits of flavoperidol alone or conjointly with other chemotherapeutic agents (thapsigargin, docetaxel, paclitaxel, gemcitabine, etc.) in treating chronic diseases (Srikumar and Padmanabhan 2016).

The chemical and structural features of flavones, such as hydroxyl (–OH) groups position, substitution of functional groups along with C_2=C_3 bond, are liable to interact with receptive sites or receptors in the tissue that are accountable for their biochemical and pharmacological properties. In general, the structural features of flavones and their relation with various therapeutic applications have been summarized as follows:

Table 4.1 The substitution pattern of hydroxyl, methoxyl, sulfate, and glycosides in different flavones

S. No	Compound	R_1	R_2	R_3	R_4	R'_1	R'_2	R'_3	R'_4
	Apigenin 7- sulfate	OH	H	OSO_3H	H	H	H	OH	H
	Apigenin 4′,7-Disulfate	OH	H	OSO_3H	H	H	H	OSO_3H	H
	Apigeninpersulfate	OSO_3H	H	OSO_3H	H	H	H	OSO_3H	H
	Acacetin	OH	H	OH	H	H	H	OCH_3	H
	Acacetin 7-sulfate	OH	H	OSO_3H	H	H	H	OCH_3	H
	Baicalein	OH	OH	OH	H	H	H	H	H
	Cirsilineol	OH	OCH_3	OCH_3	H	H	OCH_3	OH	H
	5-Demethyltangeretin	OH	OCH_3	OCH_3	OCH_3	H	H	OCH_3	H
	Diosmetin	OH	H	OH	H	H	OH	OCH_3	H
	Diosmetin 3′ -sulfate	OH	H	OH	H	H	OSO_3H	OCH_3	H
	Dracocephaloside	OH	H	OH	H	H	O-β-D-Glucopyranoside	OH	H
	Eupafolin	OH	OCH_3	OH	H	H	OH	OH	H
	Eupatilin	OH	OCH_3	OH	H	H	OCH_3	OCH_3	H
	Eupatorin	OH	OCH_3	OCH_3	H	H	OH	OCH_3	H
	Flavone 8-acetic acid	H	H	H	CH_2CO_2H	H	H	H	H
	Gardenin B	OH	OCH_3	OCH_3	OCH_3	H	H	OCH_3	H
	Glucolueolin	OH	H	O-β-D-Glucopyranoside	H	H	OH	OH	H
	Hispidulin	OH	OCH_3	OH	H	H	H	OH	H
	Jaceosidin	OH	OCH_3	OH	H	H	OCH_3	OH	H
	Luteolin 5-methyl ether	OCH_3	H	OH	H	H	OH	OH	H
	Luteolin 3′-methyl ether	OH	H	OH	H	H	OCH_3	OH	H
	Lutolin 7-Sulphate	OH	H	OSO_3H	H	H	OH	OH	H
	Luteolin 7,3′-disulfate	OH	H	OSO_3H	H	H	OSO_3H	OH	H
	Luteolin 7-sulfate-3′-rutinoside	OH	H	OSO_3H	H	H	O-rutinoside	OH	H

	Luteolinpersulfate	OSO_3H	H	OSO_3H	H	H	OSO_3H	OSO_3H	H
	Nobiletin	OCH_3	OCH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	H
	Norwogonin	OH	H	OH	OH	H	H	H	H
	Orientin	OH	H	OH	β-D -Glucopyranosyl	H	OH	OH	H
	Rhoifolin	OH	H	O-Neohesperidoside	H	H	H	OH	H
	Skullcapflavone I	OH	H	OCH_3	OCH_3	OH	H	H	H
	Thalictiin	OH	H	O-β-D-Galactopyranoside	H	H	H	OH	H
	Tricetin	OH	H	OH	H	H	OH	OH	OH
	Tricetinpersulfate	OSO_3H	H	OSO_3H	H	H	OSO_3H	OSO_3H	OSO_3H
	Tangeretin	OCH_3	OCH_3	OCH_3	OCH_3	H	H	OCH_3	H
	Wogonin	OH	H	OH	OCH_3	H	H	H	H
	Veronicastroside	OH	H	O-Neohesperidoside	H	H	OH	OH	H

1. These three key features are considered to be vital for their antioxidant activity as has been established during the structure–activity studies of flavones (Cotelle et al. 1996; Leopoldini et al. 2004):
   (a) The number of hydroxyl groups on the B ring and their configuration predicts the activity, i.e., the catechol moiety (1,2-dihydroxybenzene) or either hydroquinone moiety (1,4- dihydroxybenzene) or galloyl moiety (1,2,3-trihydroxybenzene),which causes the formation of the phenoxyl radical after the H atom donation and attributes to the high stability of the flavonoid due to the electron delocalization.
   (b) The configuration of ring C, i.e., the C_2=C_3 double bond and C_4-oxo group, permits the electron movement from the phenoxyl radicals (B ring) to the C ring;
   (c) The C_2=C_3 double bond upsurges the resonance stabilization of the molecule due to the electron displacement across it.

   Cotelle et al. have reported the antioxidant properties either by the capacity to scavenge free radicals (ring B hydroxyl groups) or to competitively inhibit xanthine oxidase (ring A hydroxyl groups). The presence of a catechol or a galloyl type moiety on the B ring appeared essential for scavenging properties, while the 3-position hydroxyl substitution with B ring substitution also displayed scavenging properties but to a lower degree. When flavones possess the hydroxyl group at position 7 in the absence of catechol or pyrogallol groups, inhibitory activity of xanthine oxidase was observed. Similarly, 6-OH substituted flavones are known to be moderately active. The existence of hydroxyl groups in the B ring, as in flavones (apigenin, luteolin), improved the nitric oxide (NO) scavenger and advanced glycation end products (AGEs) inhibition effects, while the OH group at C_3 position of ring C, as in flavonols (quercetin), was not found favorable (Crasci et al. 2018). In another report, the existence of a free catechol group in ring B and free hydroxyl (–OH) groups at positions C_5 and C_7 on ring A was found to be liable for inhibition of xanthine oxidase (XOD) activity. Luteolin showed higher XOD inhibitory activity than luteolin-6-C-glucoside, while apigenin glycoside (apigenin-6-C-glucoside-8-C-arabinoside) exhibited higher activity than the free apigenin (aglycone form). Steric effects are also found to have a stronger influence on the chemical action of flavones.
2. Casagrande and Darbon have studied the effects of various flavonoids on cell proliferation as well as cell cycle distribution in human melanoma (OCM-1) cells. The occurrence of the C_2=C_3 bond and oxy functional group at C_4 position of ring C were reported to be required for higher antiproliferative activity. Among these compounds, the existence of a hydroxyl group (–OH) at the $C_{3'}$ position of ring B (luteolin) was reported to arrest cells in the G1 phase inhibiting CDK2, while lack of this group (apigenin) blocked cells in G2 inhibiting CDK1. Both CDK2 and CDK1 were reported to be directly inhibited by flavopiridol (Casagrande and Darbon 2001).
3. The anticancer as well as anti-inflammation effects of flavonoids owing to their pro-oxidant action and electrophilic conjugation interaction with biomolecules

caused the oxidation of flavonoids into electrophilic natured quinones (*o*-quinones/*p*-quinones). These electrophilic quinone structures are very reactive toward nucleophilic groups of biomolecules, such as thiol and amino groups (proteins, glutathione). The valuable biological effects of flavonoids are also assumed due to the formation of different addition adducts by the reaction of electrophilic quinones and nucleophilic groups of biomolecules. The functionalities on the B ring, such as catechol moiety (ortho-dihyroxy), hydroquinone moiety (para-dihydroxy) or galloyl moiety (1,2,3-tridydroxy), in flavones has an imperative role in formation of electrophilic quinones through oxidation, whereas resorcinol (meta-dihydroxy) cannot readily undergo oxidization. The basic structural features, such as the occurrence of C_2=C_3 double bond, hydroxyl groups on ring A and B specifically, C_5–OH, C_7–OH, and $C_{4'}$ –OH group are liable for anti-inflammatory activity. The hydroxyl groups at ring B either on the C2′ or C3′ position reduced the activity, while the C5′ –OH group or C4′–OCH_3 on ring B abolished the activity. The hydroxy derivatives have been reported to have more potency than their corresponding methoxy derivatives (Sharma et al. 2018a; Arivudai et al. 1996; Ravishankar et al. 2013; Batra and Sharma 2013). The flavone glycosides (apigenin and luteolin 7-*O*-glucoside) were found to have no effect on TNF-α release or NF-κB activity, while the respective aglycones showed higher efficacy to reduce the above activities. Therefore, the deglycosylation enhances the absorption of dietary flavones and modulates inflammation by decreasing TNF-α and NF-κB. The compounds have the ability to inhibit NF-κB and possess both anti-inflammatory and anticancer properties (Hostetler et al. 2012). Paredes-Gonzalez et al. have described that apigenin and luteolin remarkably activate the PI3K/Nrf2/ARE system and are known to be responsible for their anti-inflammatory effects, as indicated by the suppression of lipopolysaccharide induced nitric oxide (NO), nitric oxide synthase (iNOS), and cytosolic phospholipase A2 (cPLA2). These compounds appreciably inhibited TNFα-induced NF-κB transcriptional activation, whereas they have no effect on the degradation of IκB proteins, and the nuclear translocation and DNA binding activity of NF-κB p65 was observed (Paredes Gonzalez et al. 2015).

4. Flavonoids may show a defensive role against cancer, cardiovascular diseases, and age-related degenerative diseases. They have the ability to interact with several efflux pump proteins, such as P-gp (P-glycoprotein), multidrug resistance proteins (MRP1 and MRP2), breast cancer resistance protein (BCRP), and uptake transporters, including organic anion-transporting polypeptide (OATP), organic anion transporter (OAT), and monocarboxylate transporters (MCTs) (Wang and Morris 2014).
   (a) P-gp is a member of a multidrug resistant protein family and effluxes anticancer agents from tumor cells as an energy dependent pump. The flavonoids have the ability to inhibit P-gp activity, and they are probable agents for modulation of multidrug resistance. The presence of ring B at the C_2 position and C_2=C_3double bond of ring C, as in flavones and flavonol molecules, may be responsible for the intercalation with the hydrophobic amino acid residues of P-gp. The apigenin and quercetin had greater binding affinity in comparison

with genistein, naringenin or rutin. P-gp modulators, NBD2 (C-terminal nucleotide-binding domain) contain an ATP-binding site and a close but distinctive hydrophobic steroid RU486-binding site. The SAR studies using NBD2 and cell lines recommend the presence of a double bond (planar structure), i.e., 2–3hydroxyl groups (3 and 5) and hydrophobic substituents on the A or B rings. These features are responsible for high P-gp-modulating activities, while the glycosylation causes decreased potential against the above activities (Kitagawa 2006; Zandena et al. 2005; Wang and Morris 2014). Luteolin is known to induce apoptosis in P-glycoprotein and ABCG2-expressing MDR cancer cells without any change in the transport functions of these drug transporters. It induces apoptosis and involves ROS generation, DNA damage, inhibition of NF-kB signaling pathway, activation of ATR → Chk2 → p53 signaling pathway, activation of p38 pathway, and depletion of antiapoptotic proteins. The analysis of luteolin also acknowledged specific molecular characteristics of NCI-ADR/RES and MCF-7/Mito^{R} cells that highlight their different tissue origins having therapeutic prospective to control the proliferation of MDR cancers without disturbing the physiological role of drug transporters in the body tissues (Rao et al. 2012).

(b) The structure–activity relationship regarding potency in modulating MRP1 activities specified that flavones and flavonols were more effective than flavanols, flavanolols, flavanones, and isoflavones. The glycosylation of flavonoids leads to a decline in the inhibitory activity. The required structural characteristics of flavones for high MRP1 inhibitory effectiveness are (i) the existence of two to three double bonds for a planar molecular structure, (ii) the existence of OH group at C3′ and C4′ position of the B ring, and (iii) the hydrophobic groups substitution at C4′–OH group of the B ring. The flavones with a pyrogallol group (1,2,3-trihydroxy group) on the B ring showed MRP2 inhibition (Wang and Morris 2014). Recently, Seo et al. reported that apigenin was able to oppose the drug resistance against the adriamycin-resistant breast cancer cells (MCF-7/ADR) and significantly reduced cell growth and colony formation in MCF-7/ADR cells and parental MCF-7 (Michigan Cancer Foundation-7) cells. It suppressed the mRNA expression of MDR1 and MRPs (multidrug resistance-associated proteins) along with the protein expression of P-gp (MDR1) and inhibited the production of VEGF (vascular endothelial growth factor) and MMP-9 (Matrix metallopeptidase 9), which are STAT3 (signal transducer and activator of transcription 3) target genes, in MCF-7/ADR cells. The STAT3 inhibitor S3I-201, JAK (janus associated kinase) inhibitor I, and the HIF-1α (hypoxia-inducible factor 1-alpha) inhibitor EF-24 decreased the growth of both MCF-7 and MCF-7/ADR cells (Seo et al. 2017).

(c) The higher BCRP inhibitory potential of flavonoids is because of the planarity of molecular structure owing to the existence of two or three double bonds. In addition to this, the OH group at the C_5 position of ring A and absence of this group at position C_3 of ring C as well as the ring B bonding site at C_2 position of ring C causes the enhancement of potential against inhibition of BCRP. However, the hydroxyl (OH) groups at 6, 7, 8- or 4′

position substituted with hydrophobic groups also increase inhibitory potency against BCRP, while the glycosylation reduces the BCRP-inhibiting activities (Wang and Morris 2014).

From the highlights of SAR studies, the presence of free hydroxyl groups, 4-oxo group along with the C_2=C_3 double bond of flavones are requisite features for their enzyme inhibitory activity as well as for the antioxidant activity, which suggests that this class of compounds could be attractive leads for anticancer therapies.

4.3 Biosynthesis

Biosynthetically, flavones are synthesized through the phenylpropanoid metabolic pathway (Ibrahim 2001a) from cinnamoyl-CoA, 4-coumaroyl-CoA, and caffeoyl-CoA produced from the amino acid phenylalanine, which is synthesized via the shikimate pathway (Morreel et al. 2006; Herrmann and Entus 2001; Ibrahim 2001b). CHS is a pivotal enzyme in the biosynthetic pathway of flavonoids to produce the main backbone intermediate of flavonoids commonly entitled chalcone. The CHS enzyme causes the condensation of the malonyl-CoA with either cinnamoyl-CoA, 4-coumaroyl-CoA or caffeoyl-CoA leading to the respective pinocembrin, naringenin, and eriodictyolchalcones. These are common intermediates that stereospecifically and spontaneously cyclize into respective pinocembrin, naringenin, and eriodictyol by the action of CHI. Naringenin was also converted into eriodictyol by the action of F3′H, which carried out the hydroxylation at C3′ position of naringenin. In the last step, these derivatives transformed into respective flavones by the origination of a double bond between the C_2 and C_3 positions of ring C catalyzed by FNS (Martens and Mithofer 2005; Mizuno et al. 2016; Winkel-Shirley 2001) (Fig. 4.2). The biosynthesis of flavones in *Escherichia coli* has been successfully reported by Miyahisa et al. The four genes of *Escherichia coli* cells, i.e., phenylalanine ammonia-lyase (PAL), cinnamate/4-coumarate-CoA ligase (CNL/4CL), chalcone synthase (CHS), chalcone isomerase (CHI), and acetyl-CoA carboxylase (ACC), have been used for the production of naringenin from tyrosine and pinocembrin from phenylalanine. The flavones synthase I gene from *Petroselinum crispum*, apigenin from naringenin, and chrysin from pinocembrin were successfully isolated previously (Miyahisa et al. 2006). The biosynthesis of luteolin in *Escherichia coli* and *Saccharomyces cerevisiae* has been reported from p-coumaric acid and malonate, or caffeic acid, respectively (Leonard et al. 2005; Leonard et al. 2008). Marin et al. have also reported the biosynthesis of apigenin from naringenin and luteolin from the apigenin by the action of F3′H hydroxylase in *Streptomyces albus.*

In 1939, Hutchins and Wheele reported the first reliable chemical synthesis of chrysin, apigenin, and luteolin. This method involves the reaction of substituted 2-hydroxy-4,6-dimethoxyacetophenone (I) and benzaldehyde(II a-c) in ethanolic KOH, which resulted in the formation of intermediate chalcones (III). The bromination of compounds (IIIa-c) gave rise to brominated ketones (IVa-c) by using bromine and carbon disulfide. The brominated ketones undergo cyclization by the action of potassium cyanide or at higher temperature. The demethylation and

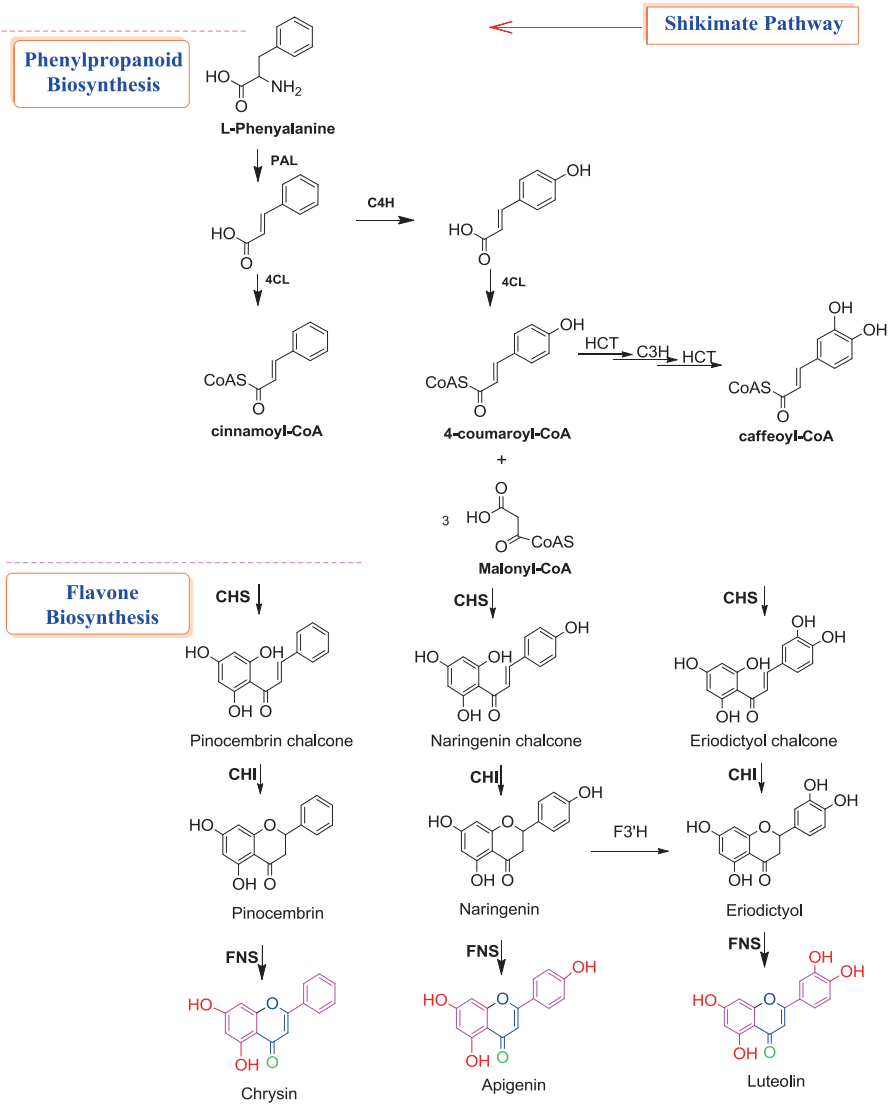

Fig. 4.2 Flavones biosynthesis pathway. The enzymes involved in the biosynthesis; phenylalanine ammonia-lyase (PAL); cinnamate-4-hydroxylase (C4H); 4-coumaroyl-CoA-ligase (4CL); *p*-coumarate 3-hydroxylase (C3H); *p*-hydroxy cinnamoyl-CoA: shikimate/quinate *p*-hydroxycinnamoyl transferase (HCT); chalcone synthase (CHS); chalconeisomerase (CHI); flavone synthase, cytochrome P450 flavone synthase (FNS)

debromination of cyclized products (Va-c) were carried out with hydroiodic acid in acetic anhydride which resulted the desired flavone products (Figs. 4.3 and 4.4). Yang and his group have also reported the synthesis of flavone (chrysin, apigenin, and luteolin) through the chalcone intermediate pathway without the bromination step. The cyclization of chalcones resulted the methylated derivative by the action

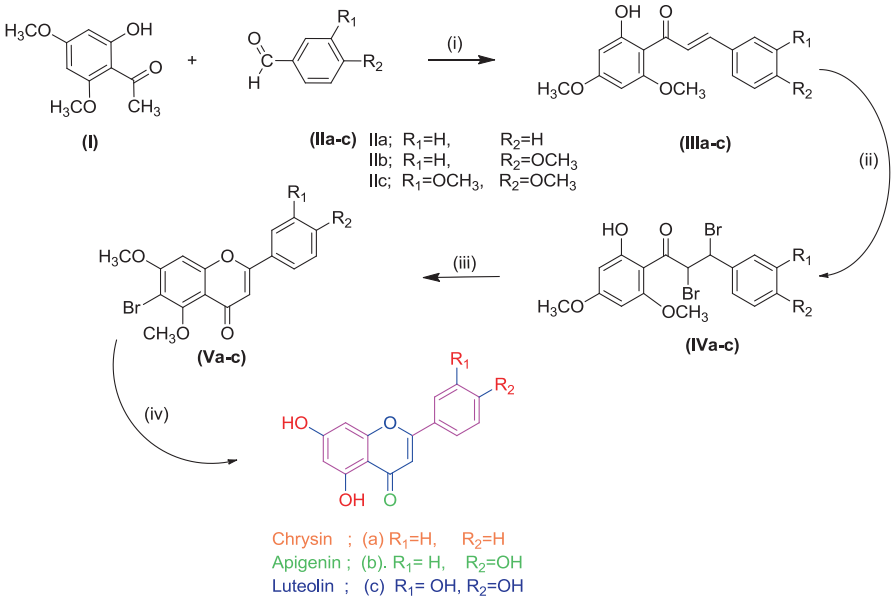

Fig. 4.3 General synthetic reaction scheme of flavones (chrysin, apigenin, luteolin) via Hutchins and Wheele's approach using 2-hydroxy-4,6-dimethoxyacetophenone (I) and benzaldehydes(IIa-c) as starting materials; (i) KOH, C_2H_5OH, (ii) Br_2, CS_2, (iii) 195 0C or KCN, C_2H_5OH, (iv) Ac_2O, HI, reflux

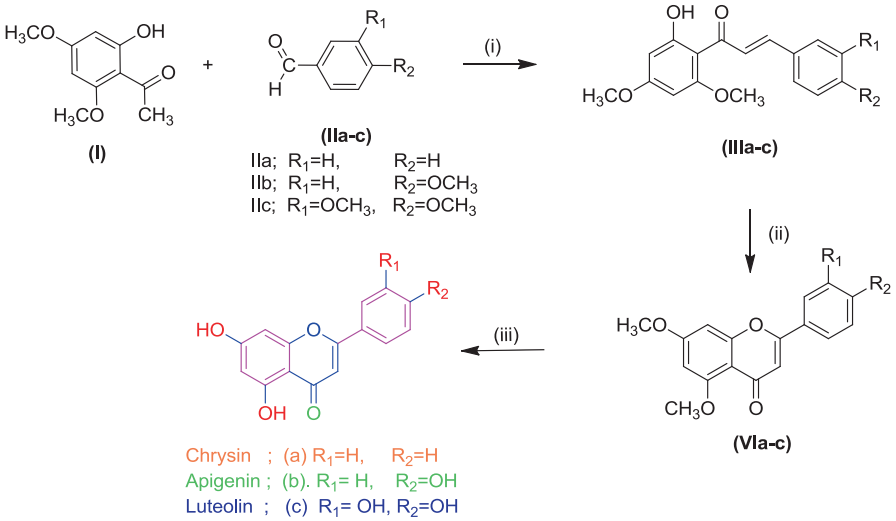

Fig. 4.4 General synthetic reaction scheme of chrysin, apigenin, and luteolin by using 2-hydroxy-4,6-dimethoxyacetophenone (I) and benzaldehydes (IIa-c) as starting materials; (i) KOH rt., (ii) DMSO, I_2, 120 °C, (iii) Py·HCl, 180 °C

of iodine with dimethylsulfoxide and then demethylation using pyridine hydrochloride led to aglycones (Wang et al. 2015; Liu et al. 2014; Zhang et al. 2014). The synthesis of flavopiridol was proposed on the basis of the reports in which compounds had a methyl group in place of a chlorophenyl ring. The proposed scheme involves the replacement of a methyl group with a chlorophenyl ring. The first step involves the reaction of trimethoxybenzene with *N*-methylpiperidone. After this step, the hydroxylation and stereocenter generation at position 3 of the piperidine moiety of trimethoxybenzene-1-methylpiperidine were carried out by using various reaction conditions, such as action of diborane, sodium borohydride, hydrogen peroxide, etc. The acetylation at 3 position of benzene ring of the intermediate was achieved by acetic anhydride and then treated with methyl 2-chlorobenzoate. The deprotonation of methoxy groups of ring A into hydroxyl groups was done by using a mixture of pyridine hydrochloride and quinolone (Kattiger et al. 1990; Naik et al. 1994) (Fig. 4.5). However, there is still a need to develop novel methods and use of existing synthetic procedures (Sharma et al. 2014a, b; Khare et al. 2016) along with reagents (Sharma et al. 2014c, 2015) for modifying the structure of bioactive molecules with improved pharmacological significance. The apigenin derivative (Ap1) possessed the strongest activity with IC50 values of 2.03 ± 0.22 μM against

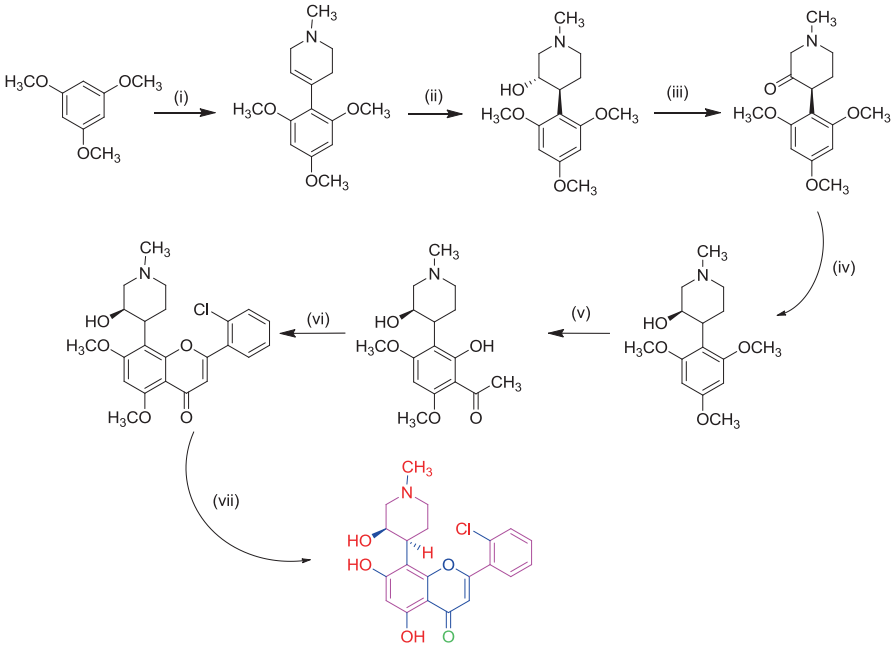

Fig. 4.5 General synthetic scheme of flavopiridol from the trimethoxy benzene via multistep synthesis; [(i); (**a**) *N*-methylpiperidone, CH_3CO_2H, (**b**) HCl gas]; [(ii); (**a**) BF_3 –OEt, Diglyme, $NaBH_4$, HCl (**b**) NaOH, H_2O_2]; (iii) CO_2Cl_2, CH_2Cl_2, DMSO, N_2, $(C_2H_5)_3N$ (iv) $NaBH_4$, C_2H_5OH (v) BF_3–OEt, CH_2Cl_2, Ac_2O (vi) methyl-2-chlorobenzoate, NaH, dioxane (vii) pyridine hydrochloride, quinolone

colorectal adenocarcinoma (HT-29) cell line and 2.25 ± 0.42 μM against leucocythemia (HL-60) cell line, which are better than 5-FU (12.92 ± 0.61 μM, 9.56 ± 0.16 μM) (Zheng et al. 2014). Liu et al. reported the chemically modified apigenin derivative (Ap2), which showed notable antiproliferative activity against human cervical (HeLa), human breast (MCF-7), human lung (A549), and human hepatocellular liver (HepG2) cancer cells lines, with the lowest IC_{50} values compared to apigenin. The chrysin derivatives (Ch1, Ch2, and Ch3) displayed the strongest activity in vitro against SGC-7901 (human gastric adenocarcinoma) and HT-29 (colorectal adenocarcinoma) cell lines with the lowest IC_{50} values (Zheng et al. 2003). Zhang et al. reported the phosphorylated chrysins ($IC_{50}$of Ch4= 10.3 μM and $IC_{50}$of Ch5=9.8 μM) were more potent and inhibited proliferation as well as induced apoptosis in HeLa cells compared to chrysin (IC_{50} =14.2 μM) (Zhang et al. 2004). In another report, the chrysin derivative (Ch6) possessed stronger activity when tested in vitro against HCT-116 (human colon), Hela (human cervical carcinoma), DU-145 (human prostate), K562 (human leukemia), and SGC-7901 (human gastric) cancer cell lines compared to 5-flourouracil and chrysin (Fig. 4.6).

4.4 Mechanistic Insight into Flavones Mediated Anticancer Effects

In the past few decades, the scientific community has revealed the immense potential of flavonoids in the treatment of dreadful diseases such as cancer (Kashyap et al. 2016a, b, 2017, 2018a, b; Sharma et al. 2018a, b). It is necessary to understand the interactions of such natural molecules with the recognized cellular target (Kashyap et al. 2016c, d, e, f, 2018b, c, d; Kashyap and Singh Tuli 2018). Flavones, such as apigenin, luteolin, chrysin, and flavoperidol, have been known to mediate both intrinsic (mitochondrial) as well as extrinsic (Fas/FasL) apoptotic cell death in cancer cells. In a study, chrysin was found to induce apoptosis in U937 cells by activating caspase 3 and the protein kinase B (Akt) signal pathway (Woo et al. 2004). Similarly, flavopiridol has shown promising in vitro anticancer activity against human chronic (CLL) lymphocytic leukaemia cells via activation of caspase-3, independently of Bcl-2, interleukin-4 (IL-4), or p53 modulation (Byrd et al. 1998). Using human hepatoma HepG2 cells, Lee et al. (2005)investigated the apoptosis inducing effect of luteiolin via translocation of Bax/Bak as well as via activation of c-Jun N-terminal kinases (JNK). Previous studies have suggested the role of these bio-metabolites to arrest the cell cycle by regulating the expression of cyclin dependent kinases (CDKs) in addition to apoptosis. It was found that flavones and flavonols caused G2/M arrest by enhancing the expression of growth arrest and DNA-damage-inducible gene β (GADD45β), 14-3-3σ and suppressing cyclin B1 in OE33 cells (Zhang et al. 2008). In another study, Zhang et al. (2009), investigated dose and time-dependent anticancer effects of flavones (luteolin, apigenin, and chrysin) and flavonols (quercetin, kaempferol, and myricetin) in human oesophageal squamous cells (KYSE-510). Mechanistic insight revealed that higher expression of p63 and p73 proteins was found to be associated with modulation of cell

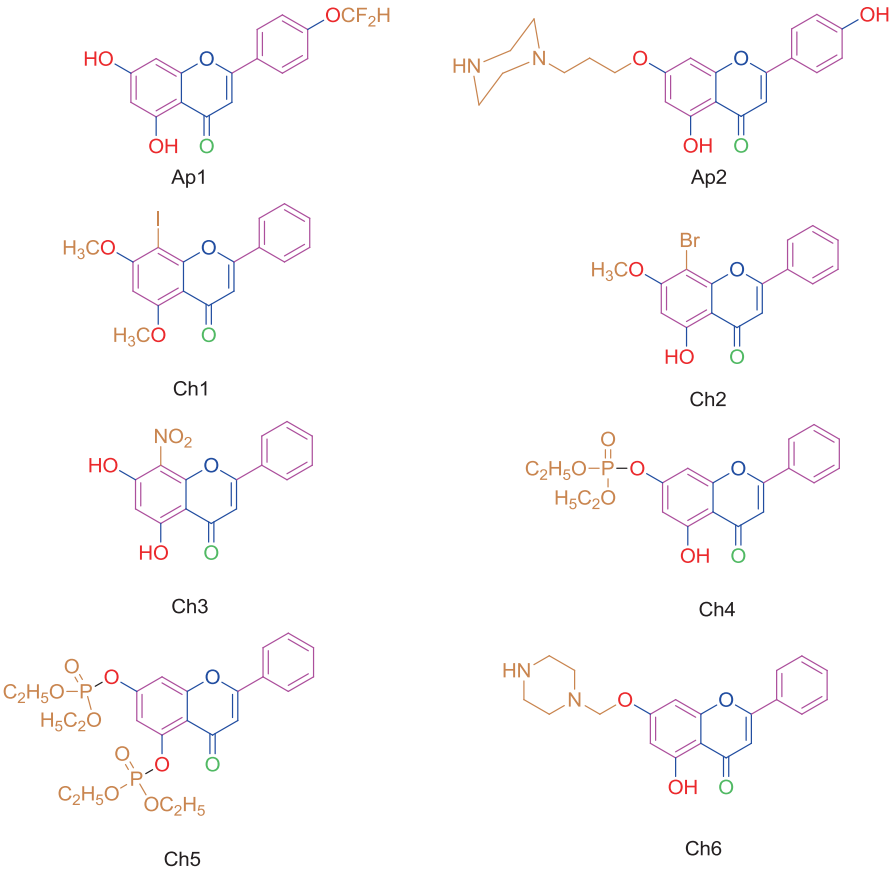

Fig. 4.6 Some of the chemically modifying derivatives of apigenin and chrysin possessing significant anticancer activities

cycle regulation via p21waf1, cyclin B1, and PIG3. Also, the expression of metastatic proteins, including matrix metallo-proteases (MMPs), has been down-regulated by these bio-metabolites. Results revealed that flavones treatment on oral squamous cell (OSCC) carcinoma led to down regulation of the expression of MMP-2 and urokinase plasminogen activator (u-PA) along with modulation of their endogenous (TIMP-2 and PAI-1) inhibitors (Yang et al. 2008). Similarly, using triple negative breast cancer (TNBC) cells, Yang et al. (2014) investigated the anti-metastatic effect of crysin via MMP-10, epithelia to mesenchymal transition (EMT), and phosphatidyl inositol 3-kinase (PI3K)/Akt pathway. Metastasis is further supported by angiogenesis, and these metabolites are well documented to inhibit neovascularization in the microenvironment of tumors. Chrysin suppresses IL-6-induced angiogenesis through modulation of the sIL-6R/gp130/JAK1/signal transducer and activator of transcription 3 (STAT3)/vascular endothelial growth factor (VEGF) signaling pathway (Lin et al. 2010). The mechanism-based antiangiogenic potential of

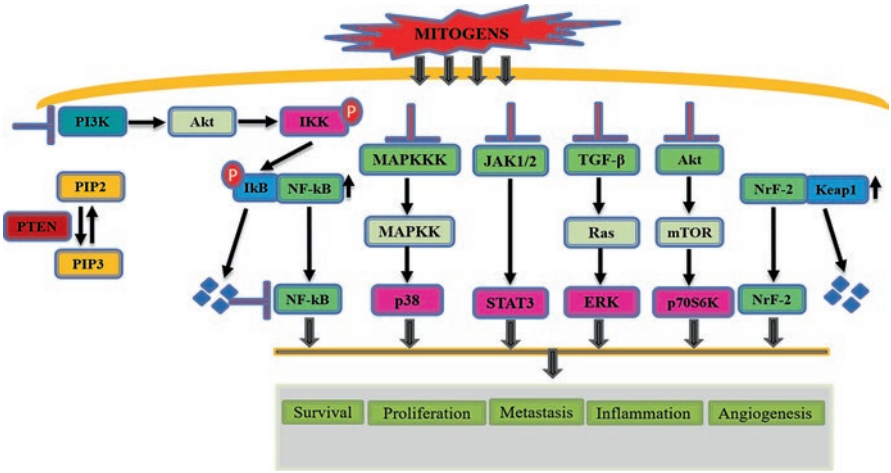

Fig. 4.7 Signaling mechanisms governed by flavones in cancer. Flavones modulate various growth factors that are involved in the signaling of both intrinsic and extrinsic apoptosis, cell cycle arrest, antimetastasis, antiangiogenesis, and anti-inflammation

other flavonoids was also observed as vascular endothelial growth factor receptor (VEGFR) and multi-kinase inhibitors of endothelial cells (Geetanjali et al. 2014). Another antitumor aspect of these metabolites can be correlated with their inhibitory effects on inflammatory mediators, such as IL-6, IL-8, interferon γ (IFN-γ),inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and tumor necrotic factor-α (TNF-α) (Chen et al. 2014; Kanai et al. 2016; Lee et al. 2016). Exploring the mechanistic insight on the mode of actions of such bioactive metabolites will help to understand the biology of cancer and further stimulate the scientific community to design novel anticancer strategies in the near future (Fig. 4.7).

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