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INVITED REVIEW

Flavonoids: structure–function and mechanisms of action and opportunities for drug development

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Abstract

Flavonoids are polyphenolic phytochemicals produced in fruits, nuts and vegetables and dietary consumption of these structurally diverse compounds is associated with multiple health benefits including increased lifespan, decreased cardiovascular problems and low rates of metabolic diseases. Preclinical studies with individual flavonoids demonstrate that these compounds exhibit anti-inflammatory and anticancer activities and they enhance the immune system. Their effectiveness in both chemoprevention and chemotherapy is associated with their targeting of multiple genes/pathways including nuclear receptors, the aryl hydrocarbon receptor (AhR), kinases, receptor tyrosine kinases and G protein-coupled receptors. However, despite the remarkable preclinical activities of flavonoids, their clinical applications have been limited and this is due, in part, to problems in drug delivery and poor bioavailability and these problems are being addressed. Further improvements that will expand clinical applications of flavonoids include mechanism-based precision medicine approaches which will identify critical mechanisms of action of individual flavonoids with optimal activities that can be used in combination therapies.

Keywords Cancer · Nuclear receptor · Nuclear translocation · Cell signaling · Apoptosis

Introduction

Flavonoids are polyphenolic phytochemicals produced in fruits, vegetables and grains and consumption of flavonoid-rich foods and nutriceuticals has been associated with a wide range of health benefits (rev. in [1–8]). Flavonoids contain a common phenylchromen-4-one scaffold which can be substituted with a phenyl ring at C2 or C3 to give the flavone and isoflavone backbone structure. Further modifications at C4 (a ketone group), C2–C3 (saturated or olefinic) plus hydroxy or methoxy substituents on the phenylchromen-4-one and phenyl rings results in formation of flavanones, flavanols, flavonols, flavones, anthocyanidins and isoflavones (Fig. 1). In addition, chalcones in which the ether ring of flavonoids has been cleaved are also considered to be members of the flavonoid family of plant polyphenolics. Flavonoids are synthesized from phenylalanine and malonyl—Co A [9, 10] and over 8000 individual flavonoids have been identified in plants [7]. Flavonoids are secondary metabolites that exhibit multiple functions in plants including their role in protecting against various internal and external stressors. Consumption of fruits and vegetables has long been associated with improved overall human health [11–14] and flavonoids have been recognized as one of the important classes of phytochemicals that enhance health benefits. Moreover, there is evidence for widespread use of individual and flavonoid mixtures as nutriceutical for maintaining health and for treatment of multiple diseases and aliments.

Effects of flavonoids on non-cancer and cancer endpoints in humans

Flavonoids have been extensively investigated for their effects on multiple non-cancer and cancer endpoints and

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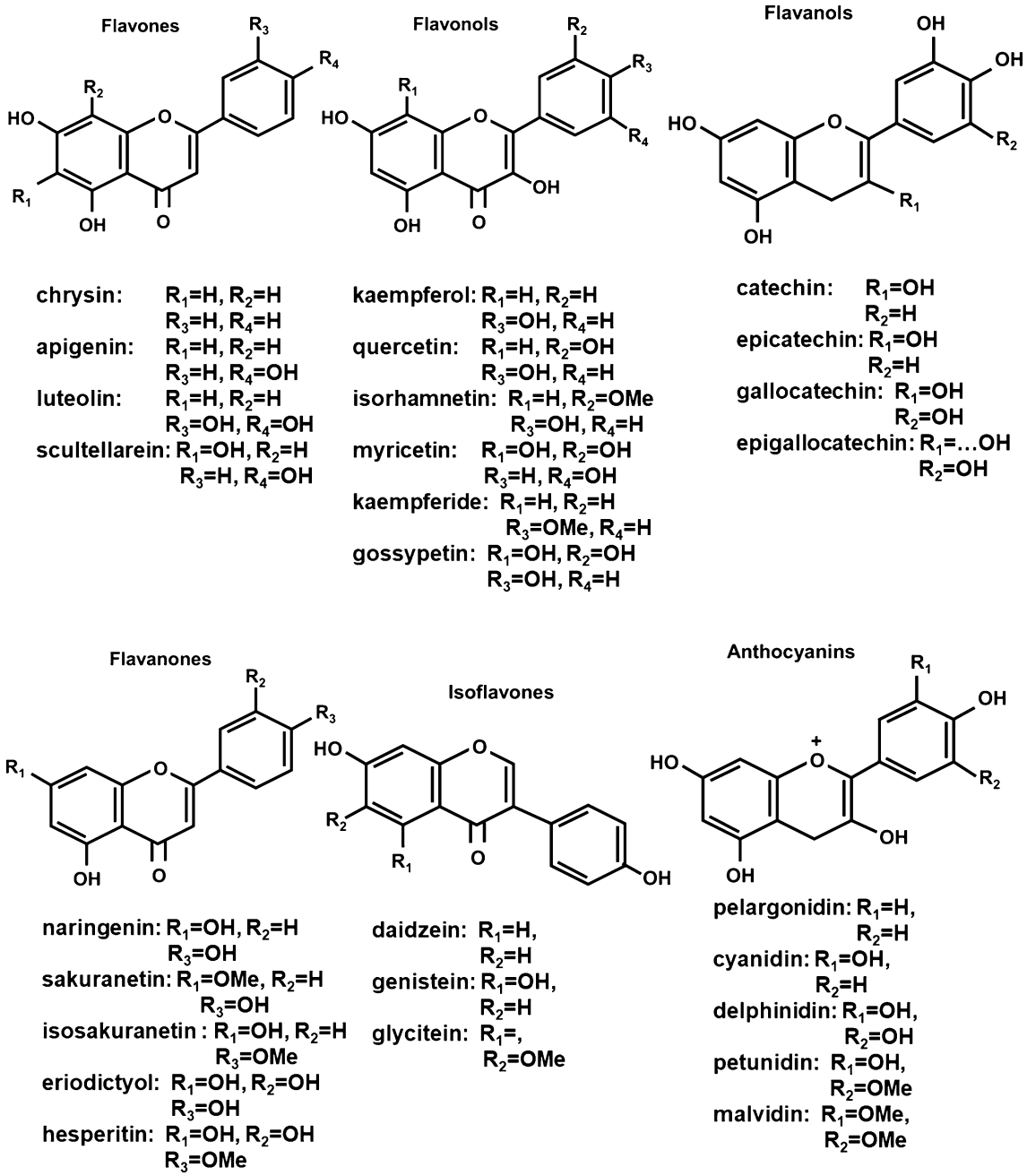

Fig. 1 Structure of flavonoids and some individual members of each class

PubMed lists over 123,000 publications dealing with these phytochemicals. Although detailed structure–activity and mechanistic studies on flavonoids are limited, the effects of these compounds have been attributed, in part to their activities as antioxidants, antimicrobial and antiviral activities, radical trapping agents and as inhibitors of key enzymes/factors such as cyclooxygenases, and acetylcholinesterase. Many studies report that flavonoids modulate expression of multiple genes and gene products that result in beneficial effects however, the mechanisms and specific polyphenolics associated with individual flavonoid-induced responses are not well defined. Among the over 123,000 citations on flavonoids, there are many primary and review articles on the health promoting effects of these compounds in several disease models of both prevention and intervention/therapeutics. Results of laboratory and preclinical studies would predict enormous health benefits from these compounds whereas human studies show modest and limited responses and some examples of effects in humans that are associated with flavonoid consumption

including aging and selected disease are summarized below.

Aging and cardiovascular disease

Biological aging is a complex process that results in the temporal deterioration of cells due to the net accumulation of damage in multiple cell types and is due, in part, to age-dependent decreases in cell repair and maintenance pathways, enhanced stress, DNA damage, mitochondrial injury and inflammation [15]. The major diseases where age is a prominent risk factor include vascular disease and atherosclerosis, joint degeneration, metabolic diseases (obesity and diabetes), skin diseases, circulatory disease (hypertension, coronary artery disease), eye diseases (macular degeneration) and neurodegenerative diseases (Alzheimer's, dementia and decreased cognitive-functions) [15]. The effects of flavonoid or polyphenolic intake on mortality as an age-dependent response has been investigated in several human studies [16–22]. A recent report on the Danish Diet Cancer and Health Cohort [16] of 56,048 participants showed that dietary intakes of approximately 500 mg/day of total flavonoids decreased overall mortality and subsequent higher intakes of up to 2000 mg/day did not further decrease mortality. The authors also reported similar effects on decreased mortality associated with dietary intakes of individual sub-classes of flavonoids including flavonols, flavanols, flavanones, flavones and anthocyanins. There was also evidence that dietary flavonoids provide some mitigation of alcohol and smoking-dependent higher rates of mortality. Interestingly there were some differences in the mortality studies in the various cohorts. For example, in the prospective Nurses' Health Study II, a comparison between the lowest and highest consumers of total flavonoids was significant only in one model even though there was lower mortality rate in the high consumer group [22]. There was a significant increase in mortality of women in the high vs. low grapefruit consuming group whereas selected flavonoid/polyphenol-rich foods such as red wine, tea, peppers, blueberries and strawberries were associated with decreased mortality. The overall consensus from most studies is that dietary flavonoids significantly lower mortality rates and can provide some protection from factors that contribute to higher rates of mortality. Many of the reports on dietary flavonoids and mortality also examine the possible association with mortality from cardiovascular diseases [9, 16–18, 20]. A high intake of dietary flavonoids was also associated with decreased cardiovascular mortality and in the Danish cohort study this association was observed for individual sub-classes of flavonoids.

Diabetes

Diabetes is another aging-related disease which in recent years has significantly increased in many countries due to diet-induced obesity. A recent meta-analysis of 18 different prospective cohort studies on polyphenol exposure and the risk of type 2 diabetes [23] reported that by comparison of extreme quintiles of intake there was an inverse association for flavonoids, flavonols, flavan-3-ols, catechins, anthocyanidins and isoflavones. A similar inverse correlation was observed for dietary intake of flavonoids and the risk of gestational diabetes mellitus [24]. A recent review summarized past and current/ongoing clinical trials on effects of various flavonoids/polyphenols on diabetes and diabetic complications including nephropathy, retinopathy, neuropathy and cardiovascular complications [25]. Although there were some indications of benefit, effects of the clinically approved and recommended use of flavonoid mixtures for treatment of diabetes and its complications were minimal despite encouraging results from animal models and cell culture studies [25, 26]. Nevertheless, meta-analysis of clinical trials (primarily with supplements) showed that flavonols and isoflavones decreased body mass index, flavonols also decreased waist circumference whereas flavonoids, flavanones and anthocyanins were not inversely associated with markers of obesity [27]. Another report (single cohort) showed that other polyphenolics correlated with decreased body mass index [28], however, flavanols were not separated out in this study. Overall, the results suggest a possible role for flavonoids in ameliorating the effects of diabetes and in diabetes prevention but identification of specific sub-classes of flavonoids that are most efficacious requires further investigation.

Neurodegeneration

There are several studies showing that consumption of flavonoid and polyphenolic foods protects against some signs and markers of neurodegeneration including various dementias and Alzheimer disease. Both intervention studies with various flavonoid-enriched foods [29–33] and evidence from the beneficial effects of the Mediterranean diet [34–37] suggest a role for these phytochemicals in neurodegenerative disease prevention. For example, decreased development of Alzheimer's dementia was associated with both strawberry and total flavonoid intake [38]. In the prospective Framingham Offspring Cohort study, individuals with the highest intake of flavonols, anthocyanins and flavonoid polymers had the lowest risk for Alzheimer disease and related dementias and this correlated changes in MRI indicators [39, 40].

Anti-inflammatory and immune cell effects

Inflammation plays an important role in many diseases and there is considerable evidence from in vitro and animal model studies that flavonoids inhibit multiple inflammatory pathways [41–43]. Many of the studies noted above are associated with flavonoid/polyphenol-mediated anti-inflammatory effects and this is confirmed in other reports [44–47]. For example, a clinical study with the citrus flavonoid hesperidin (500 mg/d for 3 weeks) decreased levels of several circulation markers of inflammation including c-reactive protein, serum amyloid A protein and soluble E-secretin [45]. Flavonoids and polyphenolics are immunomodulatory compounds and impact multiple immune cell types and the effects are highly variable and dependent on the compound, animal model and immune component [41, 43, 45, 48–51]. Reviews on the effects of flavonoids and related compounds on immune cell responses demonstrate their wide-ranging effects on immune cells and immune cell responses which include modulation of β cell and antibody production, enhancement of NK cell cytotoxicity, inhibition of Th17-dependent differentiation and NLRP3 inflammation and induction of CD8 + cells. Human intervention studies on the effects of flavonoid on immune responses give mixed results and these compounds are not routinely used for immune therapies.

Intestinal inflammation and endometriosis

Several recent reviews summarize studies showing that structurally-diverse flavonoids inhibit inflammatory bowel disease and related intestinal inflammation in laboratory animal models [52–55]. Salaritabar and coworkers reviewed and summarized effects of individual flavonoids on dextran sodium sulfate (DSS) and TNBS-and acetic acid-induced inflammation in rodent models of ulcerative colitis and Crohn's disease respectively. In the former model flavonoid that inhibit inflammation include quercetin, rutin, kaempferol, daidzein, naringenin, hesperidin, anthocyanins (cranberry) apigenin, baicalein, luteolin, fisetin, epigallocalechin-3-gallate and oligonal. TNBS-induced intestinal inflammation is inhibited by many of the same flavonoids and also morin, genistein, diosmin, tangeritin, catechiu, grape extracts and thearubigin. Rape bee pollen which contains high levels of kaempferol blocked DSS-induced colitis in mice and this included inhibition of colon shortening and decreased weight, spleen swelling and improved inflammation [56, 57]. There were also decreases in inflammatory cytokines in colon tissue with a notable decrease in IL-1β. It was also shown that there were treatment related effects on the gut microbial population with enhanced expression of Lactobacillus and decreased Allobaculum and Bacteriodes. All of these laboratory studies indicate that flavonoids and phytochemical extracts enriched in flavonoids would play an important role in preventing and treating inflammatory diseases of the intestine. There is some evidence that the Mediterranean diet which is enriched in flavonoids improves inflammatory impacts in patients with Crohn's disease and inflammatory bowel disease [58]. There was also evidence for a beneficial effect of dietary isoflavones in a cohort of Polish patients with ulcerative colitis in remission [59]. Other studies also show the beneficial effects of flavonoids [60–63], however, it was concluded "To date, clinical studies are scarce and further research with well controlled procedures and higher number of patients is essential to establish the potential therapeutic use of flavonoids" [54].

Several studies have also reported the effects of different classes of flavonoids as inhibitor of endometriosis which afflicts over 5.5 million women in the United States and 176 million worldwide. Flavonoids that inhibit pro-endometriotic pathways/genes include epigallocalechin-3-gallate, luteolin, glycosylated flavonoids from Melilotus offinalis, quercetin 3,6-dihydroxyflavone and chrysin [64–74]. For example, epigallocatechin-3-gallate (ECGC) exhibits antifibrotic properties in mouse models, established endometriotic cells and patient derived cells and this includes decreased invasion and inhibition of multiple fibrotic genes including α-smooth muscle actin [74]. One study reported that a cocktail of agents which included quercetin reduced some of the symptoms and serum markers of endometriosis (PGE2 and CA-125) [75], however, clinical applications of flavonoids for treatment of endometriosis are minimal despite promising preclinical laboratory studies.

Cancer

A pubmed search of flavonoids and cancer listed over 22,000 papers demonstrating the high level of interest and preclinical studies on the anticancer activities of these phytochemicals. Flavonoids have been widely characterized as anticancer agents via their inhibition of multiple pro-oncogenic pathways and genes in cancer cells and also to a lesser extent, their induction of tumor suppressor-like responses and genes [2, 4, 6, 12–14, 76–80]. Based on this abundance of data, results of clinical trials on the chemopreventive and chemotherapeutic effects of flavonoids are underwhelming. A recent update on flavonoids as cancer chemopreventive agents summarized results of case control and prospective studies which correlated flavonoid intake with risks for breast, lung, prostate, gastric, pancreatic head and neck, and colorectal cancers. Although there was some evidence showing that intake of total or specific flavonoids was associated with decreased risks for some cancers, these observations were not observed in all studies [14]. A large prospective study did not observe an association between flavonoid intake and colorectal cancer risk; and this was

also observed in one case control study but in two other case–control reports, there was an inverse association between flavonoid intake and risks for colorectal cancer [81–84]. Despite the extensive data on the anticancer activities of flavonoids, their applications for cancer therapy are limited and this is related, in part, to the low bioavailability of these compounds. Therapeutic trials on the effects of genistein on prostate and colorectal cancer are underway and isoflavones in combination with other agents had no effect on advanced pancreatic cancer but may have impacted PSA levels in prostate cancer patients [77, 80, 85–88].

Human studies show some benefits of flavonoids on mortality and other diseases based primarily on long term consumption of foods enriched in these compounds. However, despite the broad range of effects of flavonoids on multiple disease related pathways in preclinical studies, the therapeutic effects and ongoing clinical applications of flavonoids are not extensive. This may be due, in part, to poor bioavailability of these compounds which should improve with development of improved delivery systems [87]. Future therapeutic benefits from flavonoids may also require a more mechanistic and precision medicine approaches where specifically targeted pathways/genes have been identified and structure–activity studies have focused on using flavonoids which exhibit optimal response-specific activities. The following section will identify and briefly discuss several specific flavonoid targets that are responsible for many of the flavonoid-induced therapeutic responses. With few exceptions, the individual flavonoids that optimally modulate specific intracellular targets have not been identified.

Mechanisms of action of flavonoids

One of the important underlying mechanisms of action of dietary flavonoids and related polyphenols is associated with their inhibition of oxidative stress and related downstream responses including inflammatory diseases. Flavonoids scavenge free radicals and their subsequent damage by forming relatively stable phenoxy radicals and also by metal chelation [15, 88]. In addition, flavonoids interact with multiple gene products to inhibit their specific actions and thereby directly modulate a limited response or for kinase inhibition, the interaction could impact multiple downstream pathways.

i. Flavonoids as kinase inhibitors.

Although flavonoids directly bind many proteins and modulate their activities, their interactions with multiple kinases and subsequent effects on downstream kinases-dependent signaling have been extensively investigated (rev. in [89–94]). Genistein was among the first flavonoids identified as a receptor tyrosine kinase (RTK) inhibitor [94] and inhibited autophosphorylation of the epidermal growth factor receptor (EGFR) and it acts as a non-competitive inhibitor of histone H2B [95]. Subsequent studies show the genistein and many other flavonoids inhibit a diverse spectrum of kinases by direct interactions with these proteins and a few structure–activity studies have identified flavonoids with optimal activities. Hou and Kumamoto [91] summarized the binding of flavonoids to multiple kinases showing both similarities and differences with respect to their interactions with one or more sites in multiple kinases. For example, myricetin binds the ATP pocket of Akt1, MKK4, Fyn, P13Kγ, p38MAPK and JNK3; myricetin also binds MEK1 and JAK1. A recent study confirmed interactions of myricetin with the ATP binding sites of both p38MAPK and JNK3 in modeling studies. However, results of flavonoid-kinase docking studies show that among a series of flavonoids that bind the ATP sites of JNK3 (acacetin, velutin, chrysoeriol, luteolin and myricetin), the β ring of myricetin is oriented in the binding site in the opposite direction compared to the other flavonoids [93]. The structure-dependent binding of 16 flavonoids to 3 acidophilic Ser/Thr protein kinases, namely golgi apparatus casein kinase (G-CK), CK1 and CK2 has also been reported [96]. G-CK inhibition by flavonoids (≤ 40 μM) was minimal and some structure-dependent inhibitory effects of flavonoids on CK1 activity were observed. In contrast, at least six flavonoids inhibited CK2 with IC_{50} values ≤ 1 μM and the presence of both 7- and 4′-hydroxyl groups was a common structural feature of the active flavonoids which appear to occupy the ATP binding pocket. This is observed as an underlying mechanism of flavonoids for inhibiting multiple tyrosine kinases. However, despite the extensive evidence showing that flavonoids inhibit multiple tyrosine kinases, the clinical applications of these compounds as targeted kinase inhibitors are minimal.

ii. Flavonoid effects on membrane-bound receptors.

Several studies demonstrate that flavonoids modulate expression or activity of multiple RTKs including EGFRs, cMET, insulin-like growth factor receptor (IGFR), vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors [92, 97–106]. Many publications show that flavonoids inhibit the function of RTKs and block downstream signaling pathways, however, there is limited data on the mechanisms of flavonoid-RTK interactions. There is evidence that flavonoids mimic ATP and interact with ATP binding sites of RTKs [92] and this is also observed for kinases. Structure–activity studies among several flavonoids identified hesperetin and naringenin as HER2 tyrosine kinase inhibitors through interactions which prevented ATP binding

[99]. In contrast, apigenin modulated HER2/HER3-P13K interactions resulting in enhanced degradation of HER2 in breast cancer cells [99]. Catechins and particularly epigallocatechin -3-gallate (ECGC) are also highly effective RTK inhibitors and at least some of their activities are due to occupation of ATP binding sites. Thus, like kinases, RTK activities can be modified by flavonoids, however, the design of optimal flavonoids for kinase specific inhibition and clinical applications is minimal.

iii. Flavonoid effects on G-protein coupled receptor.

G-protein—coupled receptors (GPCR) are seven transmembrane receptors and there are over 800 GPCRs that play diverse roles in vision, taste, smell, behavior, immune responses and the nervous system. Table 1 summarizes some of the GPCRs that are modulated by flavonoids [107–137] and demonstrates that these phytochemicals can potentially influence the large class of cell membrane receptors. Development of optimal flavonoid ligands for activating/inhibiting GPCR should be an important area of development since it is estimated that GPCRs are targets for approximately 50% of all drugs that are currently being used [138]. As illustrated in Table 1, several flavonoids interact with GPR30. Hormonal signaling traditionally involves hormone-dependent activation of nuclear hormone receptors, however, induction of estrogen (ER) signaling has also been linked to activation of kinases pathways and phosphorylation of the ER. It was shown that extra nuclear ER activity was due to the membrane bound GPR30 which subsequently activates downstream kinases. Geinstein was initially identified as a GPR30 ligand and structure–activity in PC12 cells have identified several flavonoids that activate this receptor and optimization of flavonoid targeting GPR30 and other membrane receptors could be important for diverse clinical applications.

iv. Flavonoids and the Aryl Hydrocarbon Receptor (AhR).

The AhR is a basic-helix-loop-helix transcription factor that forms an active nuclear heterodimer with the AhR nuclear translocator (Arnt) protein to activate gene expression [139]. The AhR was initially discovered as the intracellular receptor that mediates the biochemical and toxic effects induced by 2,3,7,8-tetrachlorodinezo-p-dioxin (TCDD) and structurally-related halogenated aromatics [139, 140]. However, subsequent studies demonstrate that the AhR plays an important role in maintaining cellular homeostasis and in pathophysiology and this receptor also binds structurally diverse compounds including health promoting phytochemicals such as indole-3-carbinol and

Table 1 Flavonoid interactions/modulation of G-protein coupled receptors

Receptor	Flavonoid	References
EP1 (prostaglandin receptor)	EGCG (antagonist)	[107]
5-HT_{1A}	Acacetin	[108]
Parathyroid hormone receptor 1	Quercetin (ant)	[109]
Thromboxane receptors	Multiple	[110, 111]
P2Y12	Luteolin conjugate	[111]
Cannabinoid receptors (CB)	Calechins, quercetin and anthocyanadins	[112–114]
Glucogen-like peptide—1 receptor	Flavonoids myrcetin	[115]
Opiod receptor	Methoxyflavones ECGC	[116–118]
Muscarinic acetylcholine receptor	Multiple flavonoids	[119]
Opsin	Multiple flavonoids	[120]
Calcium semsing receptor	Ligustroflavone	[121]
CXCR4	Hesperidin (ant)	[122]
Free fatty acid receptor 1 (FFA1, GPR40)	Delphinidin	[123]
Muscarinic receptor	Polymethoxyflavones	[124]
Bitter taste receptors—TAS2R39	6-Methoxyflavones multiple	[125] [126]
TAS2R39/14	Isoflavones	[127]
TAS2R39/46	Tangeretin, nobiletin and related compounds	[128, 129]
GPER (GPR30)	Baicalein (ant) Genistein, daidzein ECGC, prunetin Icarin, genistein	[130, 135] [131], [132] [133, 134] [135, 137]

flavonoids [140]. Extensive structure–activity studies demonstrate that different classes of flavonoids exhibit AhR activity as evidenced by their induction of AhR responsive CYP1A1 gene expression in cell lines and animal models [141]. However, recent studies on flavones and isoflavones demonstrate that the AhR activity of these compounds is compound-, response- and cell-context dependent [142, 143]. For example; Results illustrated in Fig. 2 show the differences between isomeric isoflavones and flavones as activators of AhR-responsive CYP1A1, CYP1B1 and UGT1A1 in Caco2 colon cancer cells. The 4′,5,7-trimethoxy-isoflavone and 4′,5,7-trimethoxyflavone; the latter compound was inactive as an inducer whereas the magnitude of the isoflavone-induced response was similar to that observed for TCDD in Caco2 cells. There are clearly major differences in the AhR activity of "isomeric" flavones and isoflavones even though the only structural difference involves the site of attachment of the phenyl ring at C1 or C2. The AhR activity of these compounds was also investigated in mouse hepatocytes (YAMC cells) and although TCDD was active, minimal activity was observed for flavonoids [142, 143].

These results suggest that flavonoids are selective AhR modulators (SAhRMs) that exhibit both AhR agonist or antagonist [140]. There are several examples of flavonoid-induced health promoting activities that are AhR-responsive and many of these are associated with the gastrointestinal tract and immune system where the AhR plays a key role. In models of intestinal inflammation anthocyanidins, cardamonin and alpinetin are protective and these responses are due, in part, to the AhR and enhanced T-regulatory cell functions by naringenin, baicalin and baicalein were AhR-dependent [144–149]. Although there is extensive evidence for a role of AhR in cancer, clinical applications of AhR-active flavonoids are not ongoing.

Flavonoids and the estrogen receptor (ESR1/ERα and ESR2/ERβ)

There is extensive evidence that flavones/isoflavones and other flavonoids bind and activate/inactivate both ERα and ERβ [150–153]. Kuiper and coworkers examined binding of structurally diverse flavonoids to both ERα and ERβ, and the most active compounds were the isoflavones genistein and daidzein which preferentially bound ERβ compared to ERα [153]. With the exception of apigenin and kaempferol, most other flavonoids did not directly bind ERα and ERβ, however, among multiple studies, the estrogenic or antiestrogenic activities of flavonoids was highly variable [150–153]. The estrogenic activity of flavonoids and its impact on human health and particularly estrogen-related conditions have been extensively investigated with respect to their potential adverse vs. health promoting effects [153, 154]. Correlations between exposure to estrogenic flavonoids and enhanced disease are minimal, however, there is

Caco2 cell lines

Isoflavones	Compared with TCDD (100%)			Flavones	Compared with TCDD (100%)		
	CYP1A1	CYP1B1	UGT1A1		CYP1A1	CYP1B1	UGT1A1
4',5,7-trihydroxy (genistein)	Not induced	Not induced	Not induced	4',5,7-trihydroxy (apigenin)	8%	19%	157%
5,7-dihydroxy-4'-methoxy (biochanin A)	54%	53%	25%	5,7-dihydroxy-4'-methoxy (acacetin)	12%	12%	57%
4',5-dihydroxy-7-methoxy	Not induced	Not induced	Not induced	4',5-dihydroxy-7-methoxy	Not induced	Not induced	Not induced
4',7-dimethoxy-5-hydroxy	Not induced	Not induced	Not induced	4',7-dimethoxy-5-hydroxy	Not induced	Not induced	Not induced
4',5,7-trimethoxy	75%	100%	106%	4',5,7-trimethoxy	Not induced	Not induced	Not induced
3',4',5,7-tetramethoxy	Not induced	Not induced	Not induced	3',4',5,7-tetramethoxy	74%	24%	Not induced

Fig. 2 Summary of induction of AhR responsive CYP1A1, CYP1B1 and UGT1A1 gene expression (mRNA levels) in Caco2 cells by isomeric flavones and isoflavones with the same substitution patterns (142, 143)

an extensive literature on the contributions of dietary isoflavones to improved health outcomes. Studies show that isoflavone consumption protects against metabolic diseases, enhances cognitive function, decreases risk of coronary heart disease and is associated with decreased risks from ovarian and breast cancers [155–161]. Most of these studies correlated health benefits with total isoflavone intake and there were also correlations with individual isoflavones daidzein and genistein; however, some decreased cancer risks also correlated with the intake of other flavonoids [160]. These results demonstrate that among all the flavonoid-mediated pathways, interactions with ER and possible GPR30 lead to some of the health benefits associated with intake of this class of phytochemicals.

Flavonoids and their interactions with other nuclear receptors

The nuclear receptor (NR) superfamily contains 48 members which include steroid hormone or endocrine receptors (including ERα and ERβ), heterodimeric receptors, adopted orphan receptors, enigmatic orphans and orphan receptors [162]. NRs play a key role in maintaining cellular homeostasis and pathophysiology and the complex roles and interactions of endogenous and exogenous ligands can impact human health. As indicated above, flavonoids (including isoflavones) bind and modulate ERα- and ERβ-mediated gene expression and downstream responses and most studies indicate that dietary flavonoids enhance health. Although most NRs bind low molecular weight compounds such as flavonoids, the activity of these compounds as ligands for NRs and their potential impacts on laboratory animal models and human health have not been extensively investigated. An in vitro screening assay for flavonoid-induced activation of NR-dependent reported genes confirmed interactions with ERα/ERβ but none of the 27 flavonoids exhibited glucocorticoid receptor or thyroid hormone receptor activity [163]. Apigenin activated progesterone receptor-mediated gene expression and blocked genistein induced estrogenic responses in the uterus thus demonstrating flavonoids with opposing activities [164]. Similar results were obtained with kaempferol which binds progesterone receptor A(PRA) and also inhibits genistein-induced estrogenic response in the rodent uterus [165]. Several studies showed that flavonoids exhibited both agonist and antagonist activities as ligands for peroxisome proliferator-activated receptor γ (PPARγ) [73, 166–171]. Genistein and daidzein exhibited PPARγ agonist pro-adipogenic activities in several cell lines [73] whereas apigetrin inhibited adipogenesis in 3T3-L1 cells and down-regulated PPARγ [169]. Flavonoids also exhibited PPARγ agonist activities in cancer cells and mouse hepatocytes [172–174]. The liver X receptors (LXRα and LXRβ) are important for cholesterol metabolism and several flavonoids modulate LXR-dependent transactivation [175–177]. Structure–activity studies in Hela cells shows that quercetin (LXR α/β) and apigenin (LXRβ) are agonists whereas galangin and naringenin are antagonists [175]. The farnesoid X receptor (FXR) regulates the biosynthesis and circulation of bile acids and is a potential drug target for treating metabolic diseases. Several flavonoids act as FXR ligands and these include quercetin, EGCG, schaftoside and prenylflavonoids [178–182]. PXR and CAR are key receptors involved in the induction of drug metabolizing enzymes and flavonoids such as hydroxylated flavones, isorhamnetin, genistein, EGCG and alpinetin activate these receptors (primarily PXR) [183–187]. There is evidence of specificity among flavonoids for their differential activation of rat vs. human PXR [183, 187] and inhibition of inflammatory bowel disease in rodents by isorhamnetin was PXR-dependent [184, 187]. These studies demonstrate that NRs are prime targets of flavonoids and optimization of drug-target interactions should identify specific NR-interacting flavonoids that have potential clinical applications.

Mechanism-based applications of flavonoids—summary

There is strong evidence from human studies that flavonoids contribute to disease prevention and their overall antioxidant properties contribute to these health benefits. However, it is also evident from mechanistic studies that individual flavonoids and their mixtures modulate activity or expression of multiple genes and downstream responses. For example, Fig. 3 illustrates some of the responses reported for

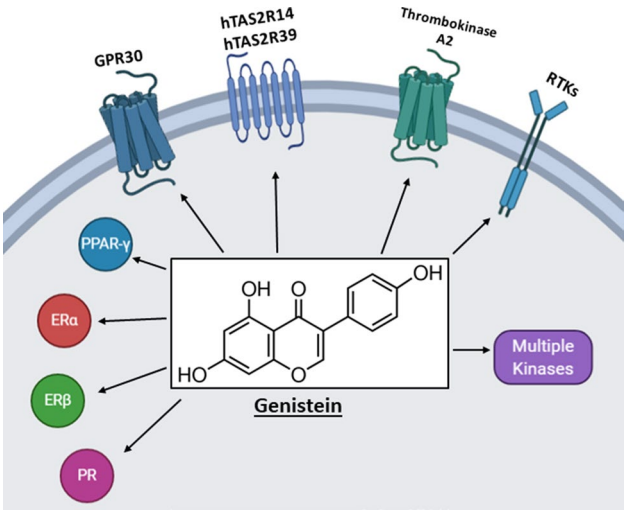

Fig. 3 Genistein inhibits/activates multiple pathways including nuclear receptors, kinases, receptor tyrosine kinases and G-protein coupled receptors (89, 91–94, 110, 111, 126, 135, 150)

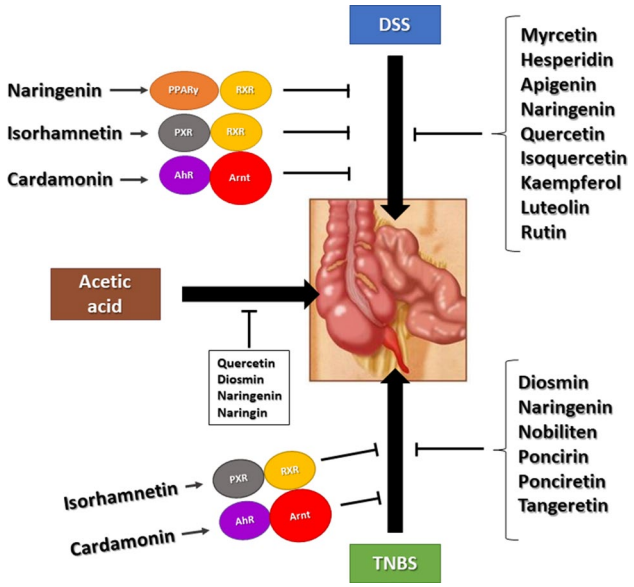

Fig. 4 Flavonoids inhibit chemical induced gut inflammation in rodent models through multiple known and unknown pathways

genistein, a major isoflavonoids component of soy-based foods which has been associated with many health benefits. Like many other flavonoids genistein interacts directly with multiple tyrosine kinases, G-protein coupled receptors and intracellular receptors. Thus, a clinical application of genistein which targets a single gene/pathway is complicated by its diverse activities and potential off-target effects. Moreover, many other flavonoids exhibit a similar pattern of effects on multiple pathways. There are also many examples of multiple flavonoids targeting a single pathway and Fig. 4 illustrates how DSS, TNBS and acetic acid-induced intestinal inflammation is inhibited by several flavonoids acting through different pathways. It is possible that some of these responses for which a specific pathway has not been identified, act through a gene/pathway which has not yet been identified. The successful development of flavonoids for clinical applications will require a more mechanistic precision medicine approach which could include the following;

1. Development of improved overall and tissue-specific delivery methods to enhance the overall bioavailability of flavonoids.
2. Response-specific mechanisms for inflammatory and age-related diseases need to be identified and utilized for chemoprevention and chemotherapy.
3. After identifying mechanism-based intracellular targets required for specific flavonoid-mediating responses, structure activity studies need to be carried out to identify the most active (optimal) flavonoid.
4. Chemopreventive and chemotherapeutic applications of flavonoids need to be maximized using combinations of active flavonoids.

Completion of the above will greatly facilitate turning the diverse and highly promising actions of flavonoids in multiple models of disease prevention into clinical applications which can be used alone and in drug combinations for treating non-cancer and cancer endpoints.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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