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REVIEW

Flavonoids as Multifunctional Phytochemicals: Structural Diversity, Pharmacological Potential and Therapeutic Prospects

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Flavonoids, a common class of polyphenolic compounds found in many plants, are known for their diverse biological activities and potential health benefits. They possess broad pharmacological actions including antioxidant, anti-inflammatory, antibacterial, antifungal, antiviral, anticancer, antidiabetic, hepatoprotective and antiatherosclerotic properties. These effects arise from their ability to neutralize free radicals, modulate inflammatory and signaling pathways, induce apoptosis in cancer cells, enhance insulin sensitivity and protect hepatic tissues. Flavonoids also play a crucial role in preventing and managing various chronic diseases, with ongoing clinical trials exploring their therapeutic potential in cancer, cardiovascular and metabolic disorders. Their multifunctional nature and natural origin make them promising candidates for the development of novel therapeutics and nutraceuticals aimed at promoting overall health and disease prevention. This review discusses the chemistry, classification, sources, mechanisms of action, absorption, metabolism and therapeutic potential of flavonoids, emphasizing their roles in oxidative stress and inflammation-related disorders. It also highlights some specific flavonoid compounds, their bioactivities and recent advances in enhancing their bioavailability for use as natural therapeutic and nutraceutical agents.

Keywords: Flavonoids, Antioxidant activity, Anti-inflammatory, Anticancer, Antidiabetic, Natural therapeutics, Nutraceuticals.

INTRODUCTION

Plants are rich sources of a wide variety of phytoconstituents including flavonoids, alkaloids, polyphenols, saponins, terpenoids and glycosides, which significantly contribute to their pharmacological properties [1]. Among these, flavonoids stand out due to their extensive biological activities and widespread presence in various plant species. Flavonoids, a class of polyphenolic compounds, are associated with many health benefits and are widely studied for their potential therapeutic uses [2]. Flavonoids derive their name from the Latin word "flavus" meaning yellow, reflecting the common occurrence of yellow pigmentation in many of these compounds [3]. They are produced through the phenylpropanoid pathway and are found in various parts of higher plants, including roots, stems, leaves, flowers and fruits. Flavonoids are a significant class of secondary plant metabolites found mainly in edible parts of plants, such as fruits, vegetables, stems, grains, bark [4] and are present in numerous plant families such as Polygonaceae, Rutaceae, Leguminosae, Lamiaceae, Apiaceae, Ginkgoaceae, Asteraceae and Umbelliferae [5]. In 1990s, researchers found that the biological activity of flavonoids has been compared to that of vitamin C, which initially led to their classification as vitamin "P" or "pycnogenol"- a total flavonoid extract from *Pinus pinaster*, which is now recognized by the Food and Drug Administration (FDA) as an edible flavonoid nutraceutical [6].

Over time, more than 10,000 flavonoids have been identified, including notable examples such as luteolin, apigenin, quercetin, kaempferol, myricetin, hesperidin, fisetin, galangin, genistein and isorhamnetin. These compounds give plants vibrant colours, especially in their leaves, flowers and fruits and play important roles in plant defense [7].

The pharmacological activities of flavonoids are also remarkably diverse. They act as antioxidants, fighting oxidative stress by scavenging free radicals, which helps prevent chronic conditions such as cardiovascular disease, cancer and neurodegenerative disorders [8]. Flavonoids also have anti-inflammatory effects by modulating inflammatory pathways,

which reduces tissue inflammation and related symptoms [9]. Their antimicrobial and antiviral properties further increase their therapeutic potential, supporting their role in preventing and treating infections [10]. Moreover, flavonoids exhibit anticancer effects by influencing cell growth, programmed cell death and metastasis, making them promising agents for cancer prevention [11]. Their antidiabetic effects involve enhancing insulin sensitivity and glucose metabolism [12], while their anticoagulant properties help lower the risk of blood clots [13]. Due to these broad health benefits, flavonoids are increasingly seen as valuable dietary supplements that support overall health and disease prevention [14]. The growing interest in natural products has increased demand for flavonoids in the medical and healthcare sectors. They are easily accessible in everyday foods such as fruits, vegetables, nuts, seeds and herbs, which contribute to a health-promoting diet [15]. Their roles as natural antioxidants and anti-inflammatory agents support their inclusion in functional foods and nutraceuticals designed to manage diseases and promote overall health. As research continues to explore their mechanisms and clinical effectiveness, flavonoids remain a vibrant area of scientific study, reflecting their potential as natural therapeutic agents [16].

Medicinal chemistry research involves the discovery of new biologically active compounds, focusing on lead compounds derived from nature that contain important heterocyclic moieties in their structure. In continuation of previous reviews [17-20], the present review aims to highlight natural flavonoid lead compounds and their associated pharmacological activities. Flavonoids and coumarins comprise the benzopyrone chemical class and chemically, flavonoid and coumarin are 2-phenylchromen-4-one and 2*H*-chromen-2-one, respectively (Fig. 1).

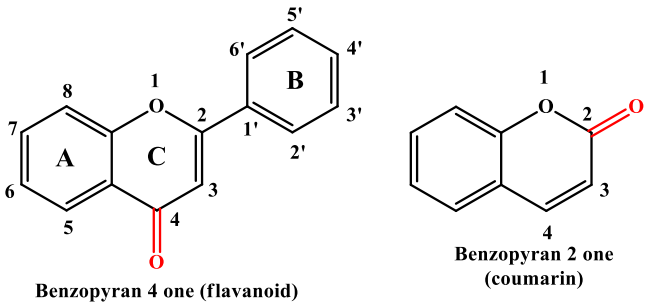


Fig. 1. Basic core structure of a flavonoid and coumarin

Their basic structure is a skeleton of diphenylpropane, namely, two benzene rings (ring A and B, see Fig. 1) linked by a three-carbon chain that forms a closed pyran ring (heterocyclic ring containing oxygen, the C ring) with the benzenic A ring. In most cases, B ring is attached to position 2 of C ring, but it can also bind in position 3 or 4; this, together with the structural features of the ring B and the patterns of glycosylation and hydroxylation of the three rings, makes the flavonoids one of the larger and more diversified groups of phytochemicals, so not only of polyphenols, in nature.

Classification of flavonoids: From a classification point of view, flavonoids are recognized as a major group of polyphenols, accounting for over 60% of dietary polyphenols [21]. They are divided into several subclasses based on structural features, mainly the position of ring B attachment, the degree of unsaturation and the oxidation of the C-ring (Fig. 1). For instance, in isoflavones, the B ring attaches at the third position of the C-ring, while in neoflavonoids, it attaches at the fourth position. Flavonoids, where the B ring is bonded at the second position of the C-ring are further classified into subclasses such as flavones, flavonols, flavan-3-ols, flavanones, isoflavonoids, catechins, neoflavonoids, flavanonols, anthocyanins and others. These classifications are mainly based on differences in the structural parameters and oxidation state of the C-ring, which affect their chemical properties and biological activity (Table-1), creating a detailed taxonomy within the flavonoid group [22].

The diverse pharmacological functions of flavonoids including antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, anti-tubercular, anticancer, antidiabetic, antiatherosclerosis, anti-hepatoprotective and enzyme inhibition effects are illustrated in Fig. 2.

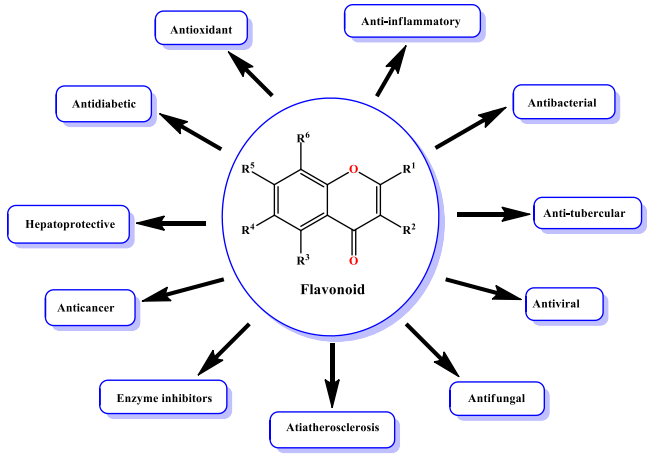
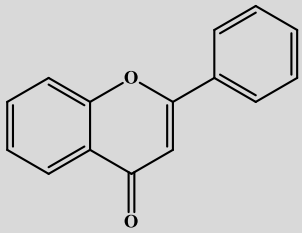
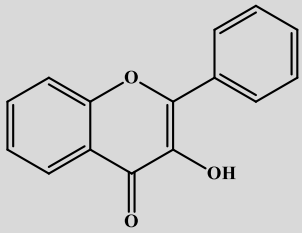
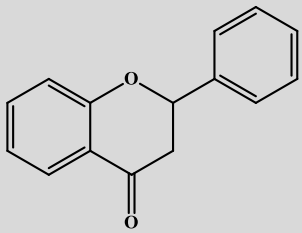
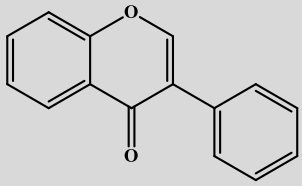
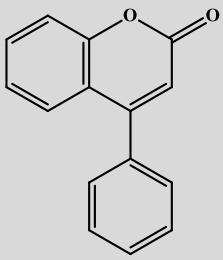
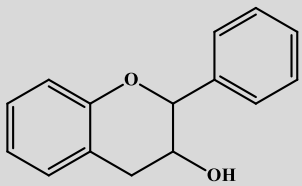
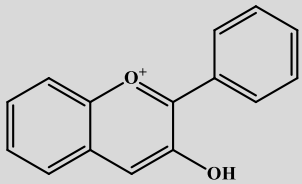


Fig. 2. Pharmacological properties of various flavonoids

Antioxidant activity: Antioxidants, especially flavonoids, play a vital role in reducing diseases related to oxidative stress by protecting cells from damage caused by oxidation [31]. The oxidative stress occurs when there is an imbalance between reactive oxygen species (ROS) or free radicals, produced during cellular processes and the body's antioxidant defenses [32]. Flavonoids are highly effective antioxidants with various mechanisms that contribute to their protective effects. They act as free radical scavengers by donating hydrogen atoms or electrons to neutralize ROS, thus preventing cellular and molecular damage [33]. Moreover, flavonoids can chelate metals such as iron and copper, which promote ROS formation, thereby blocking metal-induced oxidative stress [34]. They also inhibit enzymes like xanthine oxidase and NADPH oxidase, which produce ROS, further reducing oxidative stress [35]. *In vitro* studies have consistently demonstrated their strong antioxidant potential. For example, Oyedemi *et al.* [36] used 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay to confirm significant radical neutralization, while Firuzi *et al.* [37] employed ferric-reducing antioxidant power (FRAP) assay demonstrating their ability to reduce Fe^{3+} ions, indicating antioxidant activity. Similarly, Aderogba *et al.* [38] found

TABLE-1
CLASSIFICATION OF FLAVONOIDS, THEIR GENERAL SCAFFOLD AND EXAMPLES WITH SOURCES

Type of flavonoid	General structure	Example with reference	Source of compounds
Flavone		Apigenin, baicalein, chrysin, isorhamnetin, luteolin, nobiletin, papyriflavonol A, oroxylin A and tangeretin	Citrus fruits, celery, parsley, chamomile, mint, red pepper, apple, onion, cabbage, carrot, tomato skin and many herbs [23]
Flavonol		Fisetin, galangin, kaempferol, myricetin and quercetin	Onion, kale, lettuce, apple, berries, scallions, tomatoes, grapes, tea, red wine and berries [24]
Flavanone		Hesperidin, naringenin, naringin and pinocembrin	Grapefruit, oranges, lime juice, tomatoes, wine, bergamot, tea and grass [25]
Isoflavone		Formononetin and genistein	Soybeans or leguminous plants and microbes [26]
Neoflavonoids		Calophyllolide	Bark, leaves and seeds of the *Calophyllum inophyllum* tree [27]
Flavan-3-ols (catechins)		(+) Catechin, (-) epicatechin and (-) epigallocatechin	Black grapes, strawberries, tea, cocoa and chocolate [28]
Flavylium salts (anthocyanins)		Cyanidin, delphinidin, malvidin and peonidin	Cranberries, black currants and blackberries [29,30]

high antioxidant levels in plant extracts rich in flavonoids through multiple tests. Some herbal teas containing flavonoids, like honeybush (*Cyclopia* spp.) and rooibos (*Aspalathus linearis*), show significant antioxidant activity due to specific flavonoids such as aspalathin (**1**) and mangiferin (**2**). Honeybush tea, traditionally used to soothe respiratory issues such as cough, tuberculosis and pneumonia, is caffeine-free, low in tannins and rich in polyphenols, highlighting its health

benefits [39]. Overall, these findings support the potential of flavonoids as natural agents to combat oxidative stress and promote health [31].

Tangeretin (**3**) is a polymethoxylated flavonoid mainly found in the peel of citrus fruits, especially tangerines. It has been shown to display a wide range of pharmacological activities including antioxidant, anti-inflammatory, anticancer and neuroprotective effects. Mechanistically, tangeretin inhibits reactive oxygen species (ROS) production and p47(phox) phosphorylation, while increasing the expression of heme oxygenase-1 (HO-1) and enhancing the DNA-binding activity of nuclear factor erythroid 2-related factor 2 (Nrf2) to the antioxidant response element (ARE). Furthermore, it enhances the expression and activity of key antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) [40]. Compounds 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one (**4**) [41] and 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-8-(5-methyl-2-(prop-1-en-2-yl)-hex-4-enyl)-4*H*-chromen-4-one (**5**) have been isolated from the dried roots of *Sophora flavescens* Aiton (Leguminosae) and demonstrated antioxidant activity using the DPPH method.

Anti-inflammatory and anti-oxidative flavonoids: The oxidative stress promotes a wide range of pathological conditions including cancer, diabetes, arthritis, rheumatoid arthritis, neurodegenerative diseases and hypertension [42]. Growing evidence highlights the protective role of flavonoids, natural polyphenolic compounds, in reducing the risk of cardiovascular diseases by counteracting oxidative stress within the vascular system [43]. Flavonoids primarily function through potent antioxidant mechanisms that mitigate oxidative damage and associated inflammatory responses. As shown in Fig. 3, the development of cardiovascular disease involves a complex inflammatory cascade in which oxidative stress triggers the upregulation of enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), which catalyze the production of pro-inflammatory mediators including cytokines such as interleukins [44]. Some flavonoids, especially quercetin (**6**), have demonstrated inhibitory effects on COX and LPO enzymes, thereby reducing the inflammatory cascade and providing anti-inflammatory effects that are particularly beneficial in high-risk cardiac populations [45,46]. Research indicates that dietary polyphenols can serve as effective supportive agents in preventing or managing chronic inflammatory conditions. For example, Meng-Zhen *et al*. [47] have reported the anti-inflammatory and antioxidative effects of flavonoids in neurodegenerative diseases such as Alzheimer's and Parkinson's by reducing oxidative damage and neuroinflammation. Compounds like quercetin (**6**), found abundantly in fruits and

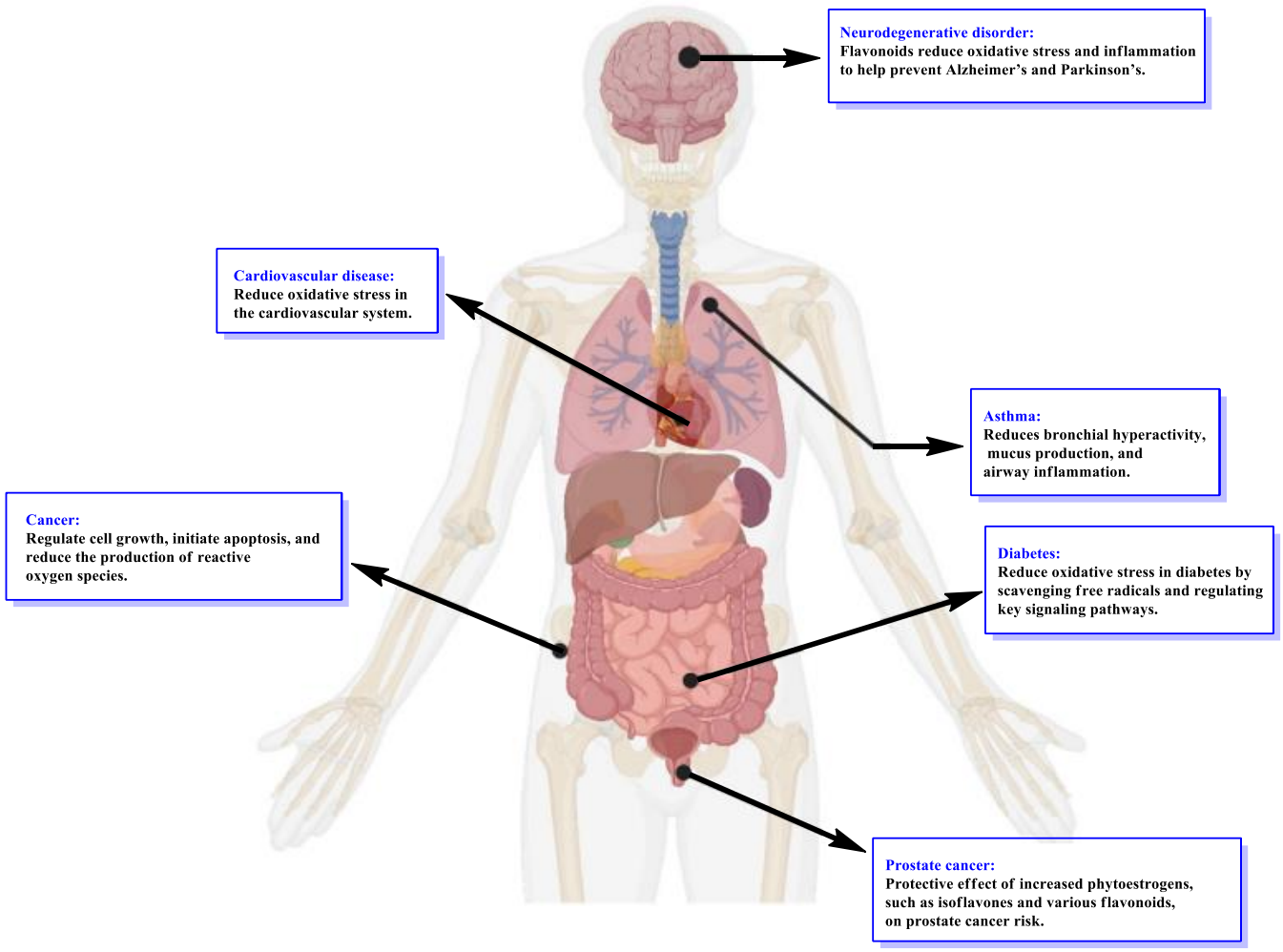


Fig. 3. Flavonoids are known to prevent oxidative stress-related disorders

vegetables, exhibit broad biological effects, including the alleviation of asthma symptoms such as mucus overproduction, bronchial hyper-responsiveness and airway inflammation. The inflammatory response is an essential protective process that occurs when tissues are damaged, invaded by pathogens, or exposed to toxic or harmful substances. It involves immune cell migration, release of mediators and the production of ROS and reactive nitrogen species (RNS) that help eliminate pathogens and promote tissue repair [48]. Normally, inflammation is temporary and resolves on its own; however, persistent inflammation due to regulatory failure can lead to chronic diseases such as obesity, cancer and neurodegeneration [49]. Flavonoids, with their anti-inflammatory and antioxidative properties, are increasingly recognized as promising therapeutic agents for these conditions. Specific flavonoids, including quercetin (**6**), apigenin (**7**), luteolin (**8**) and hesperidin (**9**), inhibit key enzyme systems such as tyrosine kinases and serine/threonine kinases, which are essential in inflammatory signaling [50].

They bind competitively at ATP-binding sites, effectively reducing kinase activity and subsequent inflammatory mediator production. Moreover, flavonoids suppress the expression of inducible nitric oxide synthase (iNOS), cyclooxygenase (COX) and lipoxygenase (LOX), enzymes responsible for creating inflammatory mediators such as nitric oxide, cytokines, prostanoids, leukotrienes and chemokines [51]. This suppression leads to decreased inflammation and tissue damage. An *in vitro* study by Elisha *et al.* [52] involving leaf extracts from nine plants confirmed their significant anti-inflammatory, antioxidant and anti-arthritic properties, highlighting the potential of flavonoids in treating autoimmune and inflammatory disorders [52]. Overall, flavonoids have a wide array of biological effects, including anti-inflammatory, antioxidant and immunomodulatory actions that make them promising candidates for developing new treatments targeting oxidative stress and chronic inflammation. Natural compounds, especially flavonoids, have gained significant attention for their neuroprotective properties, mainly due to their ability to modulate inflammatory responses involved in neurodegenerative diseases [53]. Compounds like kaempferol (**10**) and epicatechin (**11**) enhance natural antioxidant capacity, protecting tissues from oxidative injury associated with cardiovascular diseases, neurodegeneration and aging [54]. Extensive research shows that flavonoids provide neuroprotection and anti-inflammatory effects by influencing immune cell function, reducing pro-inflammatory mediators and regulating key signaling pathways. For example, studies on honey flavonoid extract (HFE) have demonstrated considerable anti-inflammatory activity in microglial cells stimulated with lipopolysaccharide (LPS). In these models, HFE at concentrations of 0.5 and 1 mg/mL effectively decreased the expression of inducible nitric oxide synthase (iNOS) at both the mRNA and protein levels, along with lowering the production of cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) [55]. These findings underscore flavonoids' ability to reduce microglial activation, a key factor in neuroinflammation. Fig. 4 illustrates the anti-inflammatory actions of flavonoids, encompassing the modulation of immune cell activity, reduction of chemokine and cyclooxygenase-2 (COX-2) expression, suppression of cytokine release and inhibition of pro-inflammatory

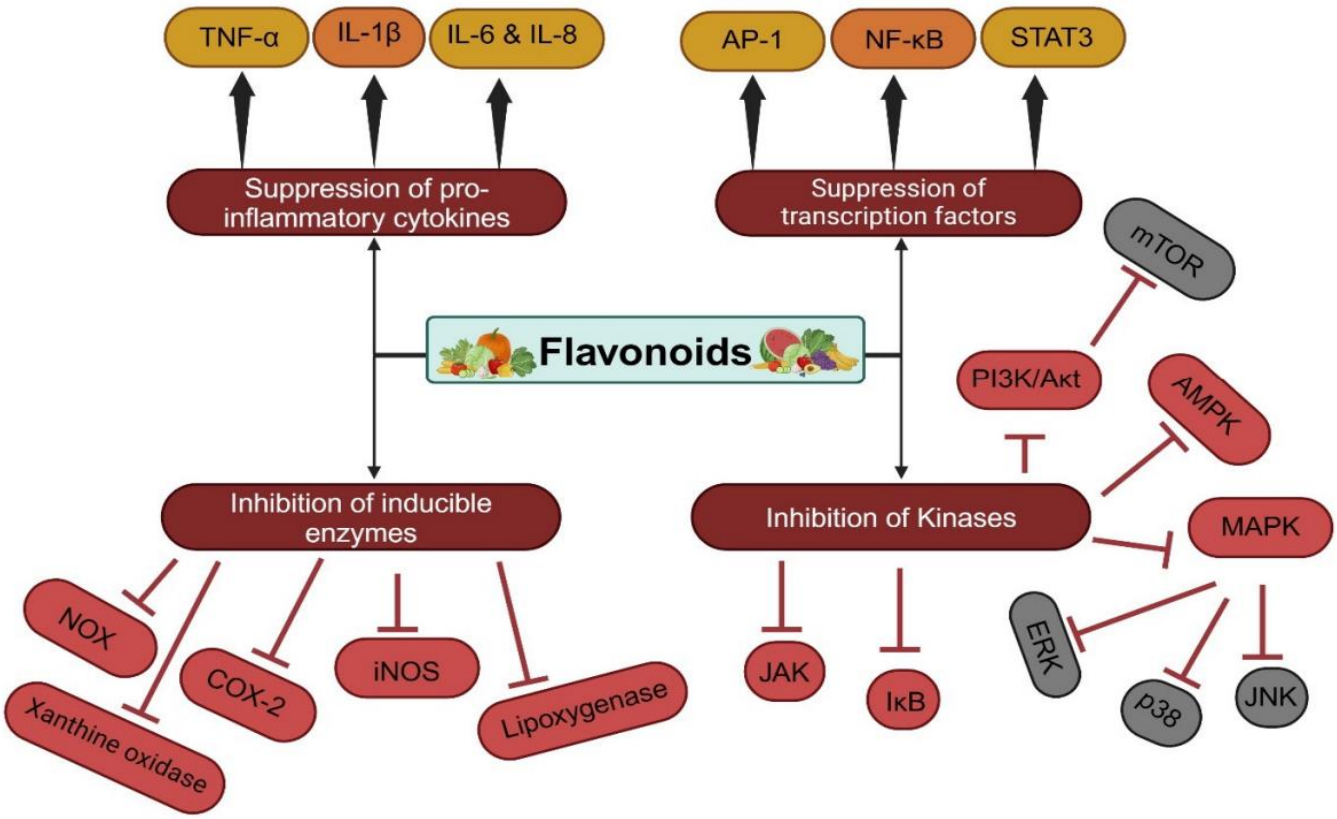


Fig. 4. The molecular targets for flavonoids in anti-inflammatory processes

transcription factors, including PI3K/Akt and IKK/JNK [56]. Recent advances focus on delivering flavonoids through encapsulation techniques, which impact their influence on cytokine activity. Encapsulated flavonoids can differentially regulate cytokines such as IL-1β, IL-6, TNF-α, IL-8 and the anti-inflammatory cytokine IL-10, depending on factors like flavonoid type, concentration, cell line and treatment duration. Encapsulation often enhances bioavailability and effectiveness, resulting in more potent modulation of inflammatory responses [57]. At the cellular level, flavonoids have various effects on oxidative stress, inflammation and apoptosis pathways, with different roles in cancer and non-cancerous cells. For example, in non-malignant cells, flavonoids generally activate the Nrf2 pathway, boosting antioxidant defenses such as glutathione, superoxide dismutase and catalase to protect cells from oxidative damage. Conversely, in cancer cells, flavonoids typically inhibit the NF-κB pathway, which is often abnormally activated in tumors, thereby decreasing cell growth, survival and metastasis [58]. This differential effect arises from the altered redox states and signaling dynamics characteristic of cancer tissues, in which high ROS levels promote tumor growth through pathways such as MAPK, PI3K/Akt and NF-κB [59,60]. Flavonoids such as quercetin (**6**) have been shown to induce apoptosis in cancer cells by modulating these pathways, lowering ROS levels and inhibiting cell growth [61,62]. Conversely, in normal cells, flavonoids help maintain redox balance, reduce oxidative stress and prevent cellular damage.

This dual role highlights the therapeutic versatility of flavonoids across various physiological and pathological conditions. Furthermore, exploring synergistic effects between flavonoids and other bioactive molecules could unlock new therapeutic options and improve their efficacy. Applying these insights to clinical strategies may lead to innovative treatments for neurodegenerative, inflammatory and oxidative stress-related diseases.

Baicalin (**12**) was extracted and purified from *Scutellaria baicalensis* and has been shown to exhibit anti-inflammatory activity [63]. Nguyen *et al.* [64] have documented the anti-inflammatory effects of calophyllolide (**13**), a compound isolated from *Calophyllum inophyllum* Linn. Calophyllolide (**13**) administration inhibited prolonged inflammatory responses by decreasing the expression of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α, while enhancing the expression of the anti-inflammatory cytokine IL-10 [64]. Karaoğlan *et al.* [65] isolated luteolin (**8**) from *Stachys lavandulifolia* (Lamiaceae) [65] and Stefano *et al.* [66] demonstrated the anti-inflammatory property of mangiferin (**2**) effects in the endothelial cells cultured *in vitro*.

Antibacterial activity: For centuries, traditional medicinal practices have used preparations containing flavonoids as the main active ingredients to treat various human diseases [67]. For instance, *Tagetes minuta* contains quercetagetin-7-arabinosyl-galactoside has been widely used in Argentine folk medicine to manage infectious illnesses [68]. The antimicrobial properties of propolis (known as "tzori" in Hebrew) are mentioned throughout the Old Testament and this natural resin was recommended by Hippocrates (460-377 BC) in ancient Greece for sores and ulcers [69]. The bioactivity of propolis mainly derives from its high flavonoid content, especially galangin (**14**) and pinocembrin (**15**) [70,71]. Similarly, Huang-chin (*S. baicalensis*) has been used both internally and externally for thousands of years in China to treat periodontal abscesses and infected oral wounds. The flavone baicalein (**16**) is considered to be the primary compound responsible for its antimicrobial effects [72].

Antifungal activity: Many ethnomedicinal plants contain various flavonoid fractions that demonstrate antifungal activity. For example, flavonoid quercetin (**6**) derived from plants has shown antifungal effects against *C. krusei* and *C. albicans*, with minimum inhibitory concentrations (MICs) of 16 and 32 μg/mL, respectively [73]. Flavonoids isolated from Brazilian traditional medicinal plants such as *Eugenia dysenterica* and *Pouteria ramiflora* have displayed potential antifungal activity against *C. famata*, *C. guilliermondii*, *C. parapsilosis*, *C. krusei* and *C. tropicalis* [74]. Two distinct flavonoids derrone (**17**) and licoflavone C (**18**) isolated from *Retama raetam* exhibited potent antifungal effects against *Candida* spp., with MICs of 7.81 and 15.62 μg/mL, respectively [75].

Well-characterized flavonoids such as apigenin (**7**), baicalein (**16**) from *S. baicalensis*, kaempferol (**10**) from propolis, myricetin (**19**) and quercetin (**6**) have been reported to possess anti-candidal properties [76,77]. Papyriflavonol A (**20**) from *Broussonetia papyrifera* was effective against *C. albicans*, with a MIC of 25 μg/mL [78].

Propolis, notably rich in flavonoids such as galangin (**14**), has demonstrated antifungal activity against dermatophytes and *Candida* spp., with galangin (**14**) showing activity against *A. flavus*, *A. tamarii*, *C. sphaerospermum*, *P. italicum* and *P. digitatum* [79]. Flavonoids like nobiletin (**21**) and hesperidin (**9**) extracted from tangerine peel have demonstrated promising activity against *Deuterophoma tracheiphila* [80]. Chlorflavonin (**22**), the first chlorine-containing flavonoid, has been produced by *A. candidus* strains and shows antifungal properties [81,82]. Quercetin (**6**) and naringenin (**23**) are recognized as potent inhibitors of *C. albicans* and *S. cerevisiae* [83]. Moreover, flavones such as baicalein (**16**) and flavonols like myricetin (**19**) exhibit prominent inhibitory effects on *Candida* species, with MIC ranges of 1.9-21 μg/mL and 3.9-64 μg/mL, respectively [84].

Antiviral activity: Epigallocatechin (**24**), a flavonoid found in tea (*Camellia sinensis* L.), is recognized for its antibacterial, antifungal and antiviral properties. Research shows that it inhibits reverse transcriptase activity, protease activity, p24, viral entry and viral production in THP-1 and H9 cells infected with HIV-1. Liposome modification further enhances its inhibitory effectiveness. In cell-free assays, a significant decrease in protease kinetics was seen after treatment with epigallocatechin (**24**). The galloyl group is believed to be essential for its antibacterial and antiviral effects [85]. Kaempferol (**10**), a common flavonoid found in many foods, showed a significant reduction in cytopathic effects (CPE) by about 88% in Vero E6 cells infected with clinical isolates of SARS-CoV-2 at a concentration of 125 μM. Moreover, *in silico* studies suggest that its main mode of action is through the inhibition of the SARS-CoV-2 $3CL^{pro}$ enzyme [86]. A biflav-

onoid called robustaflavone (**25**) from *Rhus succedanea*, exhibited strong inhibition of the HIV-1 reverse transcriptase polymerase by the *in vitro* method [87].

Anti-tubercular activity: Medicinal plants are a rich source of bioactive compounds with potential anti-tuberculosis effects [88,89]. Several flavones, flavonoids and related metabolites have been reported to show moderate activity against mycobacteria. Bioassay-guided fractionation of *Haplopappus sonorensis* led to the isolation of flavone (**26**), which inhibited the growth of *M. tuberculosis* H37Rv by 33% at a concentration of 100 μg/mL [90]. Moreover, ermanin (**27**) and compound **28**, isolated from the Mexican medicinal plant *Larrea divaricata*, exhibited minimum inhibitory concentrations (MICs) of 50 μg/mL against *M. tuberculosis* H37Rv [91].

Flavones (**29**), previously isolated from the Chilean plant *Valeriana laxiflora*, showed MICs of 46.2 μg/mL [92]. Furthermore, flavonoid (**30**), isolated from the rhizomes of *Kaempferia parviflora* collected in Thailand, demonstrated antimycobacterial activity with MIC values of 50 μg/mL. These findings highlight the strict structure-activity relationship requirements within this class of compounds for antimycobacterial efficacy [93].

Anticancer activity: Evidence-based data indicate that flavonoids have therapeutic potential for diseases, including cancer [94]. Compound Genistein (**3**), an isoflavone originally isolated from the flowering plant *Genista tinctoria* L. and is common in the Fabaceae family. It is widely studied for its potential as an anticancer agent, showing activity against various types of human cancers [95]. They exert anticancer effects by inhibiting cell proliferation, inducing apoptosis and autophagic cell death and promoting necrosis. Flavonoids can also induce cell cycle arrest, suppress the migration and invasion of cancer cells and inhibit tumor angiogenesis (Fig. 5). These actions help overcome chemoresistance, partly by modulating ROS-scavenging enzymes and regulating oxidative stress [96]. Moreover, flavonoids act as potent antioxidants by neutralizing free radicals, reducing oxidative stress and affecting cellular metabolic pathways (Fig. 3) [97,98]. Many flavonoids show favourable safety profiles and therapeutic efficacy [99]. Some of the flavonoids are under clinical trials for cancer treatment, including quercetin (**6**) for prostate cancer at phase I and apigenin (**7**) for colorectal cancer at phase II trials [100].

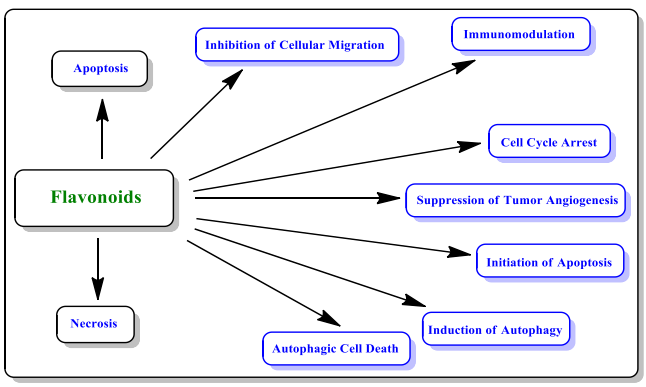


Fig. 5. Depicting different mechanisms behind the anticancer effects of flavonoids

Antidiabetic activity

Flavonoids as aldose reductase inhibitors (ARIs): Aldose reductase inhibitors help in preventing the secondary complications of diabetes by selectively blocking glucose metabolism in the polyol pathway [101]. Flavonoids such as kaempferol (**10**), hispidulin (**33**) and cirsimarin (**34**) have been shown to inhibit aldose reductase. Kim *et al.* [102] isolated various phenolic compounds from ethanolic extracts of *Paulownia coreana* bark and demonstrated their strong inhibitory effects on aldose reductase, suggesting their potential for managing diabetic complications.

Flavonoids as α-glucosidase inhibitors: α-Glucosidase inhibitors are promising agents for managing postprandial hyperglycemia and are a key focus in developing new antidiabetic flavonoids. Due to their ability to inhibit α-glucosidase activity, many flavonoids have been identified as effective inhibitors. Compounds like isorhamnetin (**35**), quercetin (**6**), apigenin (**7**), luteolin (**8**), kaempferol (**10**), naringenin (**23**) and rutin (**36**), have demonstrated significant inhibitory effects on α-glucosidase, highlighting their potential as therapeutic agents for controlling postprandial glucose levels and managing diabetes [103].

Flavonoids as SGLT-II inhibitors: Compounds such as apigenin (**7**), myricetin (**19**), quercetin (**6**) and epigallocatechin (**24**) have been shown to reduce hyperglycemia by inhibiting SGLT-1 [104]. Later, selective SGLT-2 inhibitors of natural origin were extracted from methanolic extracts of *Sophora flavescens* including formononetin (**37**), sophoraflavanone (**38**) and kurarinone (**39**) [105,106].

Flavonoids as potent glycogen phosphorylase inhibitors (GPIs): An additional promising method for reducing hyperglycemia involves inhibiting glycogen phosphorylase [107], an enzyme that catalyzes glycogenolysis to create glucose-1-phosphate, which then enters glycolytic pathways for energy production [108]. Flavonoids such as luteolin (**8**) and rutin (**36**), have been identified as effective inhibitors of glycogen phosphorylase, potentially decreasing excessive gluconeogenesis and glucose release [109].

Flavonoids as xanthine oxidase inhibitors: Xanthine oxidase inhibitors show strong potential for treating diabetes by preventing free radical formation. Many planar flavonoids, such as flavones and flavonols, including luteolin (**8**), kaempferol (**10**), quercetin (**6**), myricetin (**19**) and silybin (**40**), effectively inhibit xanthine oxidase activity. Numerous studies have been conducted to evaluate the antidiabetic potential of flavonoids based on their ability to inhibit xanthine oxidase. In this context, Guimaraes *et al*. [110] examined the protective role of rutin (**36**), a flavonoid, in reducing myocardial dysfunction in diabetic rats by inhibiting xanthine oxidase activity and decreasing oxidative stress.

Flavonoids as insulin secretagogues: Flavonoids, especially anthocyanins, act as insulin secretagogues, a property attributed to the presence of hydroxy groups on ring B [111], which enhances their ability to stimulate insulin release. Their insulinotropic activity further increases with more hydroxy groups on ring B. Strong evidence, including research by Zhang & Liu [112] shows that kaempferol (**10**) has antidiabetic effects by supporting pancreatic β-cell health and improving insulin secretion.

Flavonoids as DPP-4 inhibitor: Recently, dipeptidyl peptidase-4 (DPP-4) inhibitors have attracted significant attention because of their ability to prevent the breakdown of endogenous incretins like GLP-1 and GIP, thereby enhancing insulin secretion and reducing glucagon release postprandially. Several flavonoids, including kaempferol (**10**) and quercetin (**6**), have demonstrated effective DPP-4 inhibitory activity. This activity is linked to the presence of catechol or hydroxy groups in the appropriate configuration on ring B, the double bond between C2 and C3 and a keto group at the C4 position [113].

Hepatoprotective activity: Flavonoids exert hepatoprotective effects through multiple mechanisms, primarily by reducing oxidative stress and modulating inflammatory responses [114]. The liver, highly susceptible to reactive oxygen species (ROS), plays a crucial role in various liver diseases, often caused by exposure to toxic chemicals such as carbon tetrachloride, D-galactosamine, aflatoxins, chlorinated hydrocarbons and drugs like acetaminophen, as well as viral infections (Hepatitis A, B, E), autoimmune conditions and excessive alcohol consumption [115]. Non-alcoholic fatty liver disease (NAFLD), characterized by hepatic fat accumulation (> 5%) without significant alcohol intake, is the most common chronic liver disorder worldwide [116]. It includes simple steatosis and non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma [117]. Oxidative damage from lipid buildup, insulin resistance and increased lipolysis contributes to mitochondrial dysfunction, inflammation and fibrosis [118]. Flavonoids such as apigenin (**7**), luteolin (**8**) and naringin (**41**), enhance antioxidant defenses (*e.g.* superoxide dismutase, catalase) [119], inhibit pro-inflammatory mediators (*e.g.*, TNF-α, NF-κB) [120,121] and protecting against toxins like D-GalN/LPS-induced liver injury [122]. Naringin (**41**) was first identified by DeVry in 1857 [123] from grapefruit and found numerous pharmacological benefits such as anti-inflammatory, anti-osteoporosis, antioxidant properties, *etc*. [124].

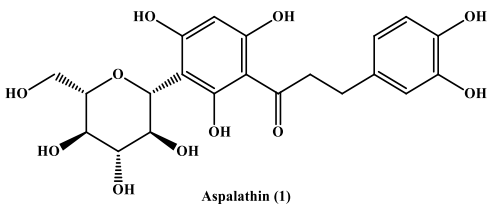
Antiatherosclerotic activity: Atherosclerosis is a chronic, lipid-driven and inflammatory condition marked by thickening of the arterial intima, stiffening and progressive narrowing of the lumen. This process underlies major cardiovascular events such as myocardial infarction, ischemic stroke and peripheral artery disease. Plant-derived flavonoids have gained significant interest due to their potential to combat atherosclerosis: many *in vitro* studies and animal model experiments show that compounds like quercetin (**6**), kaempferol (**10**), myricetin (**19**), naringenin (**23**), rutin (**36**), fisetin (**42**) and catechin (**43**), have lipid-lowering, antioxidant, anti-inflammatory and anti-atherogenic effects [125].

Quercetin (**6**) has attracted substantial interest due to its multiple protective effects on cardiometabolic health. In experimental hypertension, quercetin (**6**) improves endothelium-dependent vasorelaxation in the aorta, lowers systolic blood pressure and reduces cardiac hypertrophy and proteinuria [126,127]. In diet-induced obesity models, quercetin (**6**) administration decreases body weight, visceral and subcutaneous fat deposits and hepatic steatosis, along with suppressing the expression of peroxisome proliferator-activated receptor-γ (PPARγ) and sterol regulatory element-binding protein (SREBP); the downregulation of PPARγ aligns with decreased adipogenesis [128,129]. Leaves of *Morus alba*, which contain quercetin (**6**) as the main flavonol, significantly reduced atherosclerotic lesion formation in LDL receptor–deficient mice. This effect is due to increased resistance of LDL to oxidative modification, resulting in a 52% reduction in lesion area [130]. Short-term dietary quercetin (**6**) also exhibits anti-inflammatory and antiatherogenic effects: a 14-day treatment eliminated cytokine-induced expression of human C-reactive protein (CRP) in transgenic mice, linking quercetin (**6**) to the suppression of a key inflammatory marker for cardiovascular disease [131]. Histopathological studies further show regression of aortic atherosclerosis in hypercholesterolemic rabbits after quercetin (**6**) supplementation [132].

Rutin (**36**) isolated from *Dimorphandra mollis* lowered plasma triglycerides in hypercholesterolemic hamsters without affecting high-density lipoprotein (HDL) or total cholesterol and was found to be non-toxic with no significant changes in total leukocyte, mononuclear or granulocyte counts compared to controls [133]. Mauray *et al.* [134] conducted an *in vitro* study on 24-week-old Apo E-deficient mice, observing a reduction in atherosclerosis development and lipid deposits with the use of anthocyanins, specifically cyanidin (**44**), delphinidin (**45**), malvidin (**46**) and peonidin (**47**).

Flavonoids as enzyme inhibitors: Amentoflavone (**48**), a biflavonoid composed of two apigenin (**7**) units linked at C-8 and C-3′, is found in plants such as *Chamaecyparis obtusa*, *Ginkgo biloba*, *Hypericum perforatum* [135] and *Xerophyta plicata* [136]. It displays various bioactivities and is a strong inhibitor of cytochrome P450 isoforms CYP3A4 and CYP2C9. By inhibiting these enzymes, amentoflavone (**48**) can significantly affect the hepatic metabolism of co-administered drugs, creating a risk for important drug-drug interactions [137]. Oroxylin A (5,7-dihydroxy-6-methoxyflavone) (**49**) is an O-methylated flavone derived from *Scutellaria baicalensis* and the root bark of *Oroxylum indicum* [138]. Pharmacological studies have shown that oroxylin A (**49**) inhibits dopamine reuptake, indicating activity at dopamine transporter–mediated uptake pathways in neuropharmacological assays [139], a property that may contribute to its potential effects on the central nervous system.

Prenylflavonoids: 8-Prenylnaringenin (**50**) is a prenylated flavonoid found mainly in hop plants (*Humulus lupulus*), which belong to the Cannabaceae family. Although hops are traditionally used in brewing beer, research has identified 8-prenylnaringenin′s strong phytoestrogenic activity, prompting investigations into its potential therapeutic applications. These include alleviating menopausal symptoms, supporting bone health and even exhibiting anticancer effects. However, concerns remain about its possible side effects due to its high estrogenic activity, making it an ongoing focus of research to understand whether it is beneficial or harmful [140]. Sophoraflavanone G (**51**) is a flavonoid compound isolated from *Sophora flavescens Ait*., a plant species in the Fabaceae (legume) family that is well-known in traditional Chinese medicine. The root of *S. flavescens* has traditionally been used to treat various conditions, including liver inflammation, jaundice and fever. Sophoraflavanone G, as an identified active constituent, has attracted research attention for its demons-



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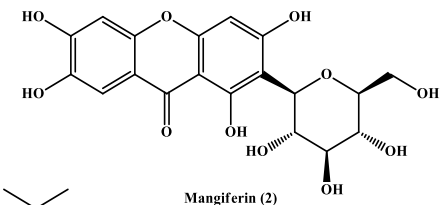
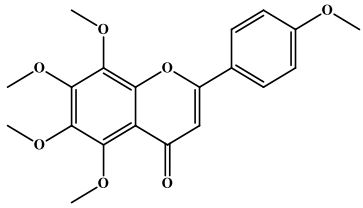
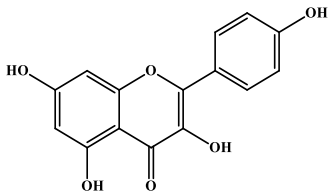


Mangiferin (2)



Tangeretin (3)



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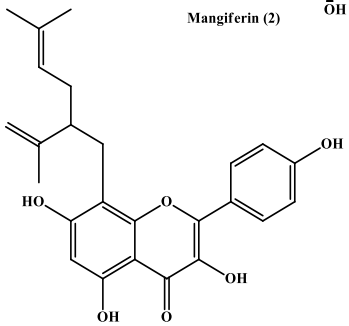

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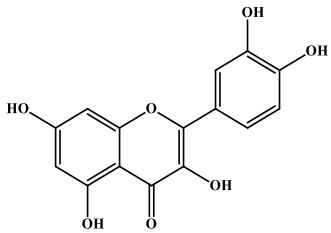
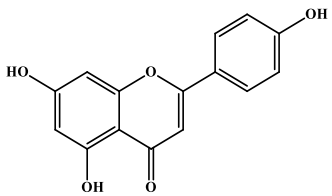
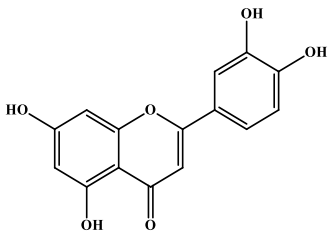


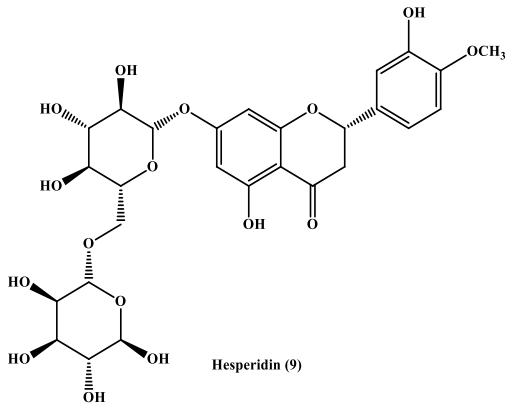
Quercetin (6)



Apigenin (7)



Luteolin (8)



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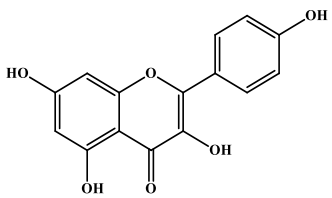
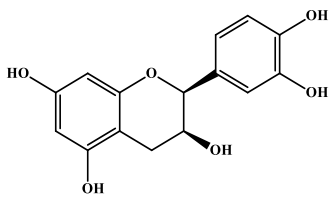
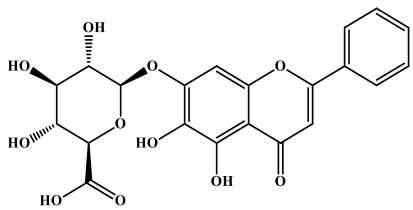


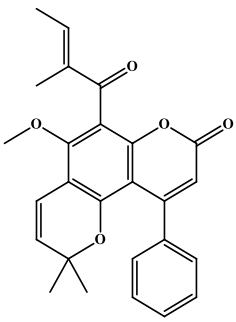
Kaempferol (10)



(-) Epicatechin (11)



Baicalin (12)



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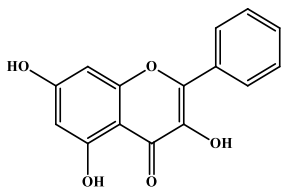
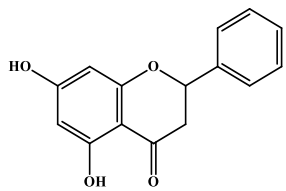


Galangin (14)



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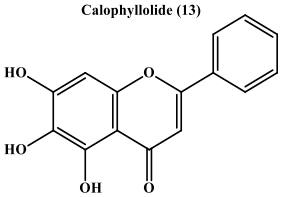
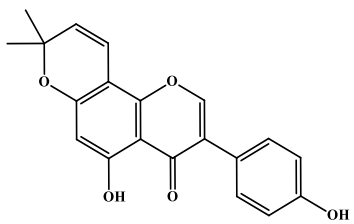


Baicalein (16)



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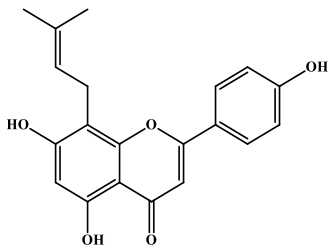
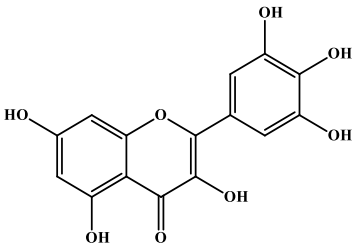


Licoflavone C (18)



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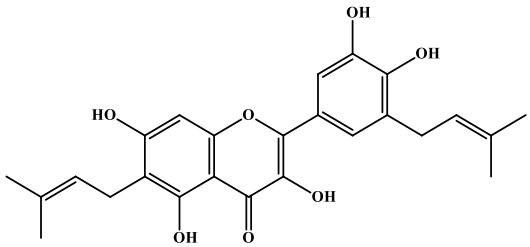
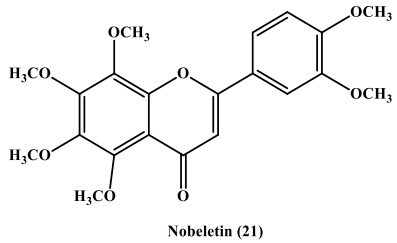


Papyriflavonol A (20)



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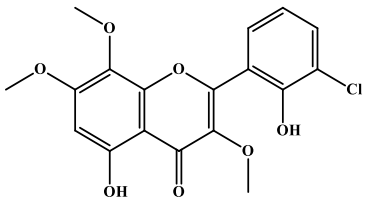

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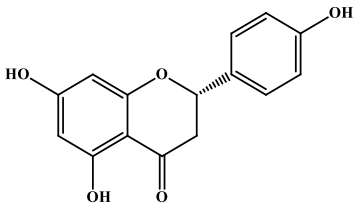
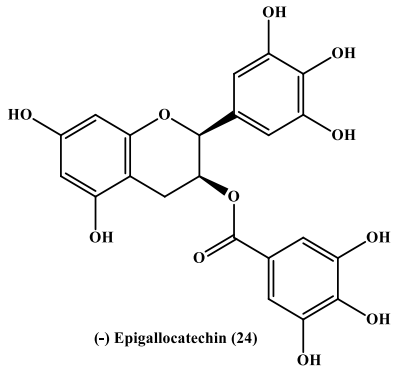
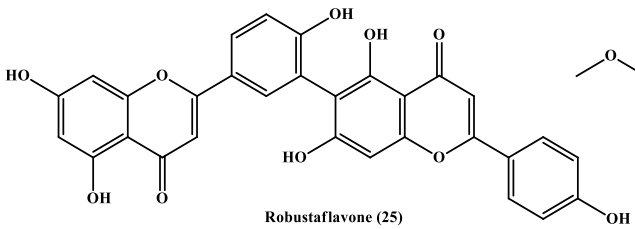


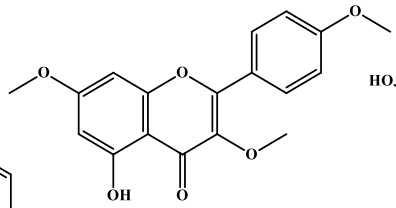
Naringenin (23)



(-) Epigallocatechin (24)



Robustaflavone (25)



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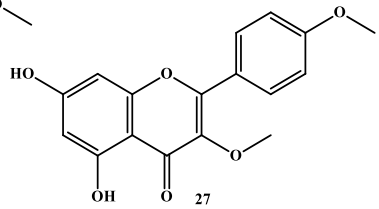

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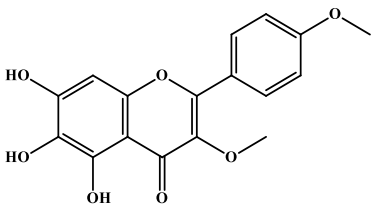

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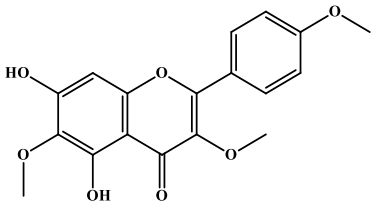

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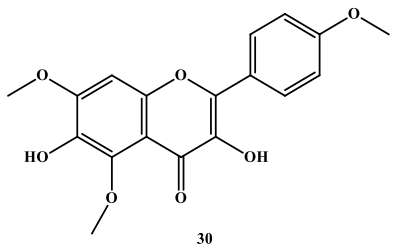

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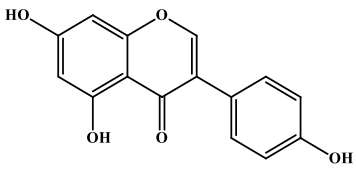
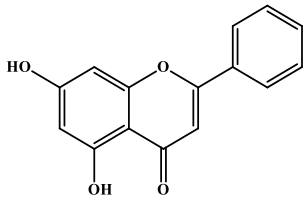
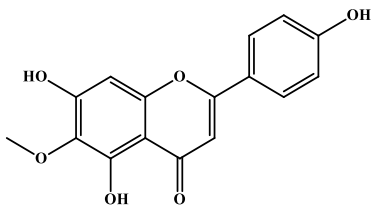


Genistein (31)



Chrysin (32)



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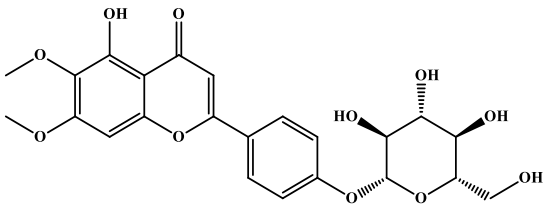

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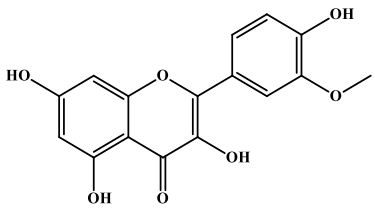

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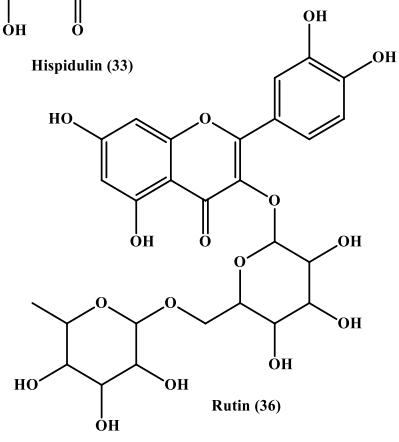
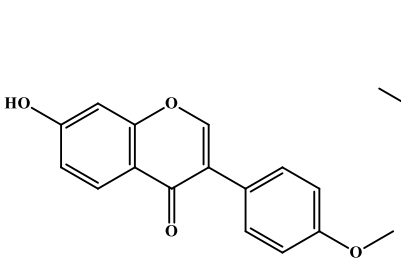


Rutin (36)



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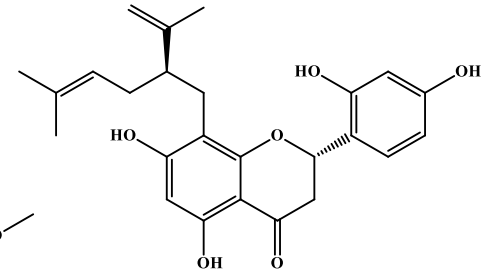
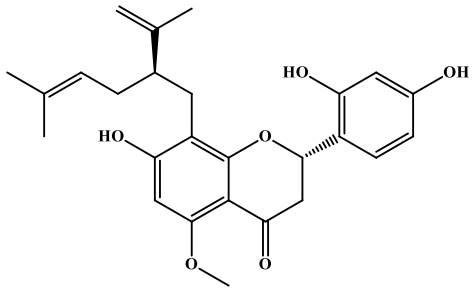
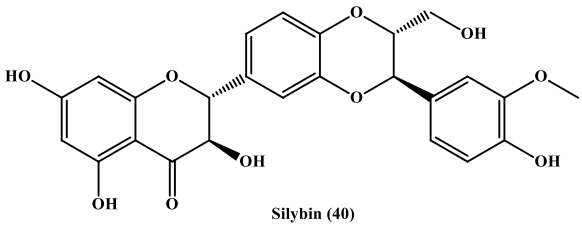


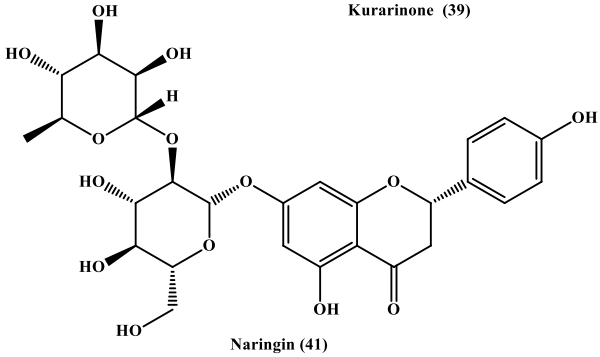
Sophoraflavanone (38)



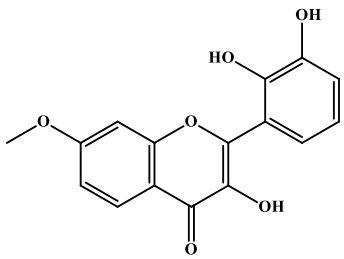
Kurarinone (39)



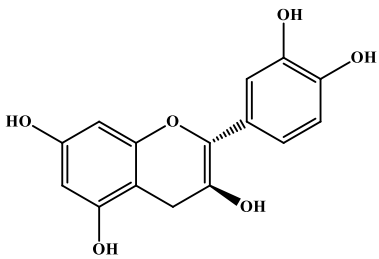
Silybin (40)



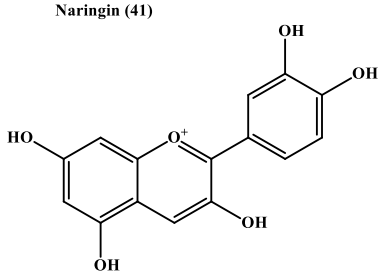
Naringin (41)



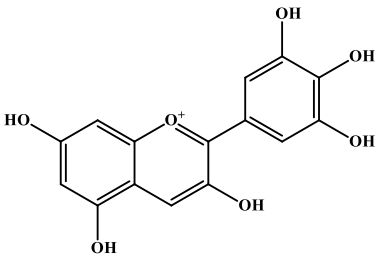
Fisetin (42)



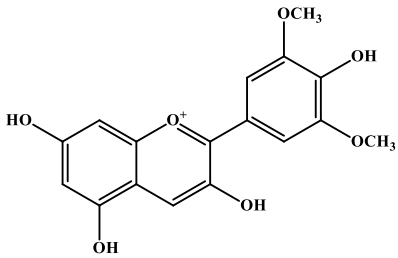
Catechin (43)



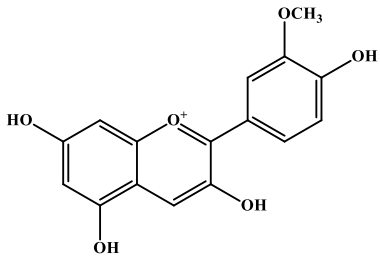
Cyanidin (44)



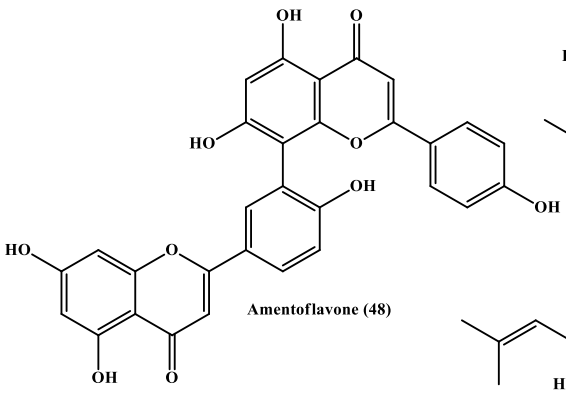
Delphinidin (45)



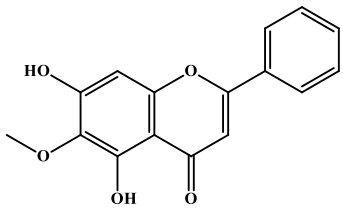
Malvidin (46)



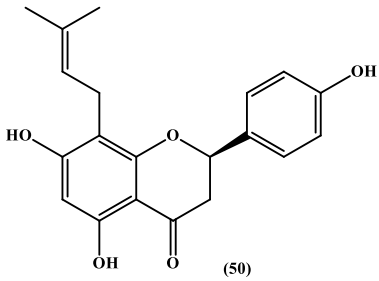
Peonidin (47)



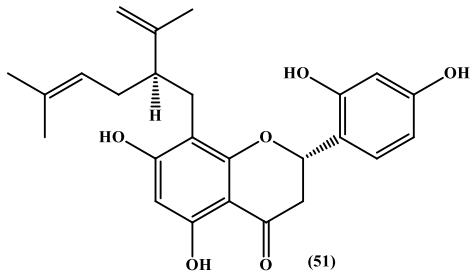
Amentoflavone (48)



Oroxylin A (49)



(50)



(51)

trated anti-inflammatory and anti-tumor properties. *In vivo* and *in vitro* studies suggest that SG may improve asthma symptoms by modulating the immune response and reducing oxidative stress, suggesting its potential to manage inflammatory disorders [141].

Absorption and metabolism of flavonoids: The small intestine is the main site of drug absorption. Flavonoid aglycones, owing to their small size and high hydrophobicity, can be absorbed directly by villous epithelial cells *via* passive diffusion [142]. However, the absorption rates differ due to structural variations and the way flavonoids respond to the intestinal pH gradient. In Caco-2 cell models, an acidic environment supports flavonoid permeation. Quercetin (**6**) absorption is highly sensitive to pH, whereas genistein (**3**) and apigenin (**7**) show less pH dependence. Another study showed that the absorption of quercetin (**6**), luteolin (**8**), apigenin (**b**) and genistein (**3**) decreases as pH increases to 5.5. This suggests that the number and position of hydroxyl groups on the B-ring of aglycone (Fig. 6) largely influence absorption. Flavonoid glycosides, which are more hydrophilic and heavier due to glycosyl conjugation, are generally not absorbed in the small intestine unless intestinal bacteria first break them down. The number and type of glycosyl linkage are key factors affecting glycoside absorption. In a study with human volunteers, taking quercetin (**6**) with rutin (**36**) led to quercetin (**6**) reaching maximum blood levels that were over 20 times higher than quercetin (**6**) alone, with a tenfold faster C_{max}. This highlights the complex relationship between flavonoid structure, glycolsylation and absorption [143].

Flavonoid glycosides need to undergo biotransformation into aglycones, followed by further metabolism into phenolic acids. This process is mediated by intestinal microbial enzymes such as β-glucosidase, α-rhamnosidase and β-glucuronidase [144]. After absorption, the liver is a key site for flavonoid metabolism, where sulfated, glutathionylated and O-methylated derivatives are the main structural forms. Glutathione and sulfonate conjugates are mainly found in the small intestine and liver, whereas O-methylation is limited to β-cyclocatechol flavonoids [145]. Hepatic flavonoid metabolism primarily occurs through oxidation and conjugation reactions. Cytochrome P450 enzymes catalyze oxidation reactions [146], while conjugation involves attaching polar functional groups (*e.g.* hydroxyl) to the parent compound or Phase I oxidation metabolites, under the action of catalytic enzymes, to form endogenous substrates. The major hepatic conjugation pathways for flavonoids include glucuronidation, sulfation and methylation [147].

Conclusion

Flavonoids are a diverse and essential group of plant derived compounds with a wide range of health-related properties. Their common presence in edible plants and their complex mechanisms of action make them promising options for developing natural medicines and dietary supplements. This review highlights the versatility of flavonoids in combating various chronic diseases. Their strong antioxidant and anti-inflammatory effects help protect against cardiovascular diseases, neurodegenerative disorders and other conditions caused by oxidative stress. The anticancer abilities of flavonoids, such as their capacity to trigger apoptosis, slow tumor growth and overcome resistance to chemotherapy, emphasize their potential in cancer treatment. Moreover, their antidiabetic and liver-protective effects provide valuable approaches for managing metabolic and liver diseases. Although flavonoids show promising therapeutic potential, more research is needed to understand fully their benefits. Future studies should be aimed to clarify how individual flavonoids work at the molecular level and improve their bioavailability and effectiveness. Ongoing clinical trials and advances in flavonoid research offer hope for translating their potential into real therapeutic applications. By utilizing these natural compounds, one can develop new strategies to prevent and treat chronic illnesses, improve human health and support overall well-being.

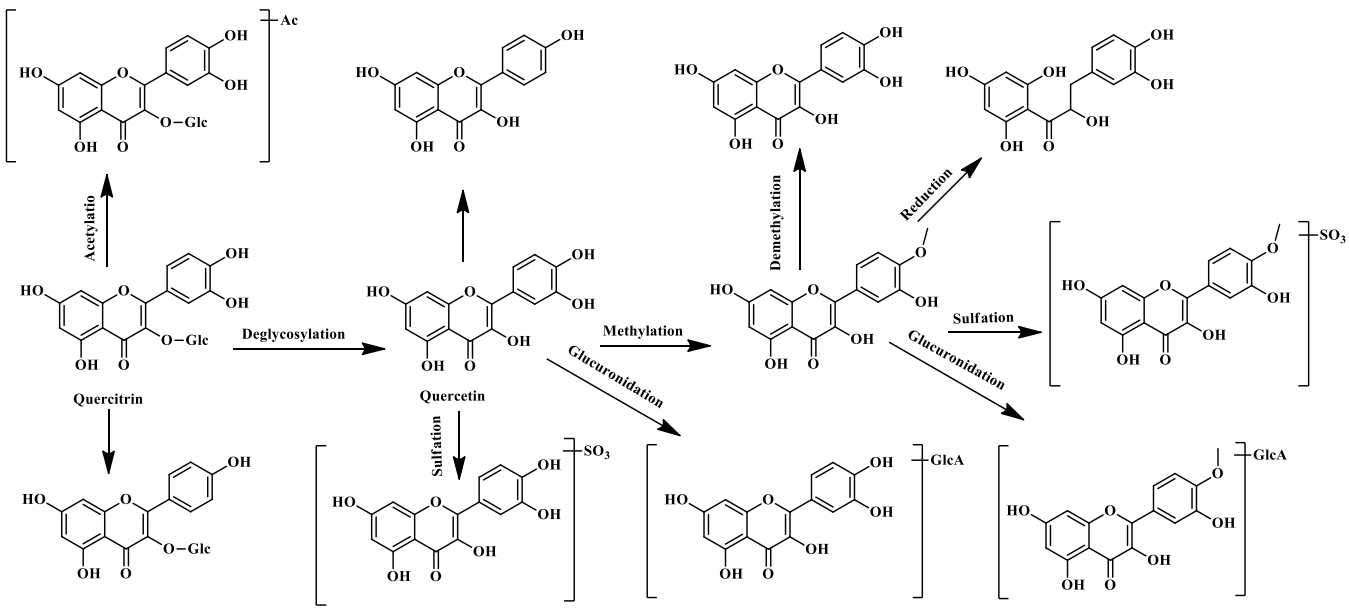


Fig. 6. Main metabolic pathways of quercitrin and quercetin in rats and gut flora *in vitro*

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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